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# COLLECTED REPRINTS

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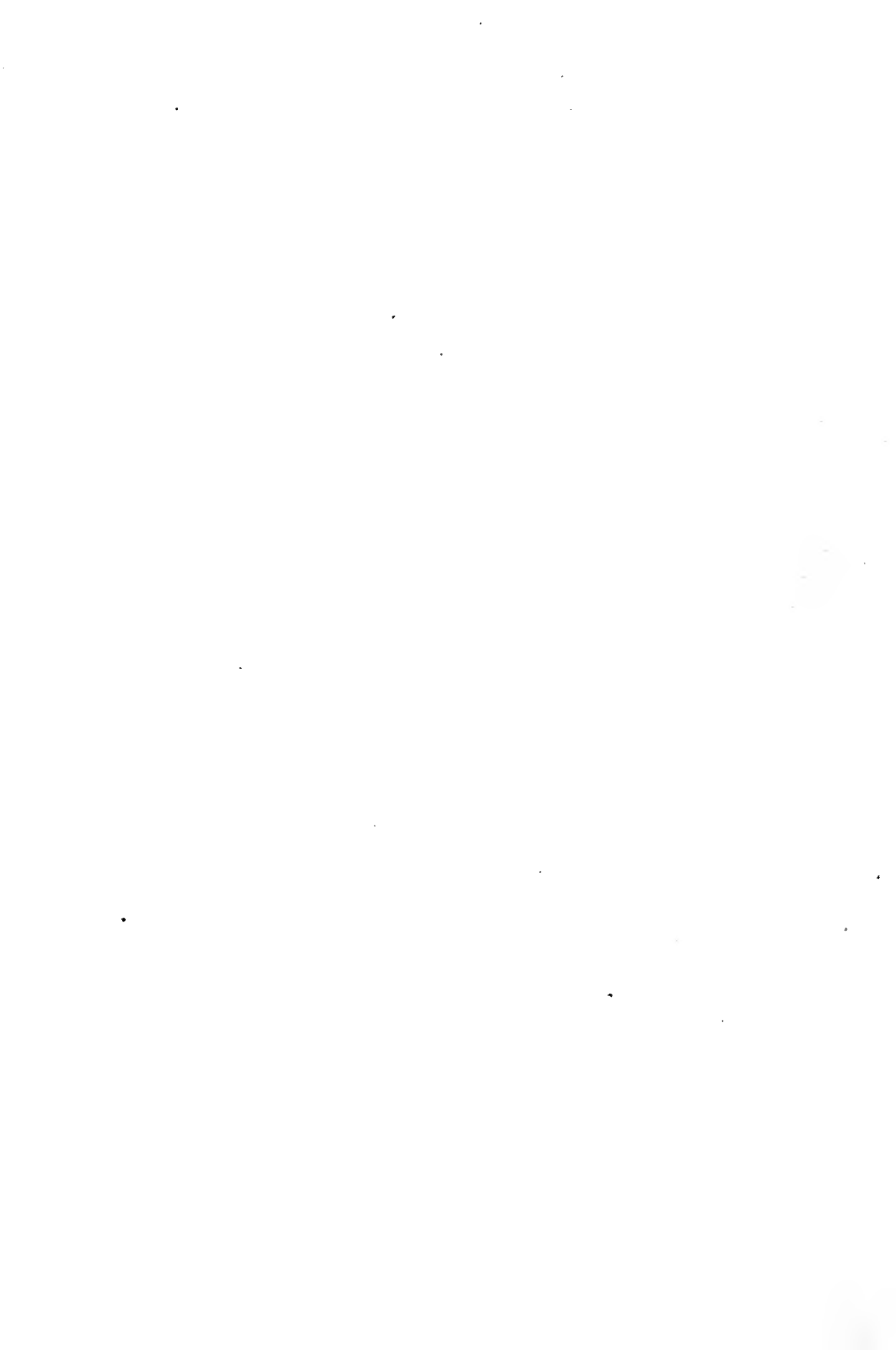
## Preface

**T**HIS volume is a collection of reprints of papers by the staff of Montefiore Hospital for Chronic Diseases in New York City. It is the intention of the Board of Directors to collect these reprints annually for limited distribution, so a brief reference to the character and present medical organization of this Hospital may be appropriate.

This institution was founded about thirty-five years ago as a Home for Chronic Invalids, but during the last few years it has become increasingly clear to its Directors and other Officers that it might serve the community in a broader capacity both as regards the present and the future by becoming a hospital for the study and treatment of sub-acute and chronic diseases. The importance of the problems of chronic diseases is becoming progressively more obvious both to the profession and to the public as the prevention and control of infectious and contagious diseases increase.

Accordingly, two years ago the professional work of the hospital was reorganized and now comprises the following divisions: (1) Cancer (including therapeutic and research departments); (2) Laboratory (including bacteriological, serological, chemical, pathological and physiological departments); (3) Medical (including cardio-vascular, gastro-intestinal, metabolic, general medical and dermatological departments); (4) Neurological (including neuropathology); (5) Surgical (including orthopedic, laryngological, ophthalmological, gynecological and neurosurgical departments); (6) Tuberculosis (including the country sanatorium at Bedford Hills).

It is believed that by grouping the clinical facilities and the research activities in this way and by co-ordinating the work of the several divisions, a closer co-operation, a greater interest and a more systematic study of the problems involved in the control and treatment of chronic diseases may be brought about—a field with which Montefiore Hospital has always been identified and with which the public is becoming more and more concerned.



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THE NATURE OF THE SO-CALLED  
"CAPILLARY PULSE"

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## THE NATURE OF THE SO-CALLED "CAPILLARY PULSE"

ERNST P. BOAS, M.D.

NEW YORK

The "capillary pulse" has been of interest to clinicians ever since Quincke<sup>1</sup> first called attention to it in 1868. Nothing, however, has been added to his original description of the condition, nor to his discussion of the probable mechanism by which it is brought about. Two observers before Quincke noted the phenomenon in isolated cases, but failed to appreciate the frequency of its occurrence or its significance. Lebert<sup>2</sup> cites the case of a patient with an aortic aneurysm who exhibited systolic flushing and diastolic paling of the cheeks. Ascherson<sup>3</sup> observed a child 7 years of age with varicella following scarlatina, in whom the papules and the bases of the vesicles reddened in diastole and paled in systole. This was very evident for four days, but after that it was only demonstrable when the skin about the lesion was stretched. Both authors attributed the phenomenon to a pulsation of the capillaries. It was Quincke, however, who observed the flushing and paling of the tissues under the finger nail not only in aortic insufficiency, but in a variety of other conditions. In patients with incompetent aortic valves it is most manifest, but it can be observed in many normal individuals. Quincke calls to mind that ordinarily, because of the elasticity of the arteries, the blood flows through the capillaries in a continuous stream; but that with venous obstruction, or with a marked lowering of the blood pressure associated with a slow pulse rate, the capillary flow may become pulsatile. A marked relaxation of the arterial wall may have the same effect. Thus Claude Bernard explained the pulsation of the capillaries and veins of the submaxillary gland which he observed on stimulation of the chorda tympani. In a later paper Quincke<sup>4</sup> emphasizes that a great difference between the systolic and diastolic pressures is essential for the visualization of the capillary pulse. He observed the phenomenon in anemic individuals, and in those with low blood pressure, an overactive heart, and a pulse

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\* From the Medical Division of the Montefiore Hospital for Chronic Diseases

1. Quincke, H.: Beobachtungen ueber Capillar und Venenpuls, Berl. klin. Wehnschr. **5**:357, 1868.

2. Lebert: Handb. der praktischen Medicin, Ed. 3, **1**:746, 1863.

3. Ascherson: Variola Versicolor, Medizin. Ztg. d. Ver. f. Heilk. in Preussen, 1834.

4. Quincke, H.: Ueber Capillarpuls und Centripetalen Venenpuls, Berl. klin. Wehnschr. **27**:263, 1890.

of the collapsing type, as well as in those with a leaking aortic valve. In his first paper Quinke described the pulsation under the finger nail, both with and without the application of gentle pressure. Subsequently, however, he noted it on the mucous membrane of the lip, when compressed with a glass slide, and on the skin of the forehead after it had been rubbed with a blunt object. When a patient exhibiting this phenomenon presents a skin lesion, such as erysipelas or urticaria, the pulsation becomes very evident.

Quinke's observations and conclusions have been generally confirmed and accepted, and we find in most textbooks of medicine, as well as of physiology, a presentation of the views first set forth by him fifty-three years ago. Lombard<sup>5</sup> in 1912 described a method by which the human capillaries can be studied directly under the microscope, but in the United States little use has been made of his observations, save by Danzer and Hooker,<sup>6</sup> who devised a method of measuring the capillary pressure, based on this principle. If a drop of glycerin or castor oil be applied to the skin at the base of the finger nail, and this area be then studied through the microscope under direct illumination, with a magnification of from 40 to 80 diameters, the capillary loops are beautifully visualized. Not only can the architecture of the capillary bed be studied, but the blood flow can be observed almost as well as in the classical demonstration of the capillary circulation in the web of the frog's foot. For details of technic, Danzer and Hooker's article, as well as of Weiss'<sup>7</sup> studies should be consulted.

While engaged in a study of the capillary morphology and blood pressure in a series of many different types of cases, I had the opportunity to observe the capillaries in eleven patients who exhibited a well marked clinical capillary pulsation under the finger nail. The capillaries in these cases were studied most assiduously under all kinds of conditions, and in no instance was a pulsatory stream of the blood in the capillaries seen.

*Method.*—A description of the method employed will be in place. A drop of clear castor oil is placed on the dorsum of a finger just below the nail bed, and the finger is then placed on the finger rest of Danzer and Hooker's microcapillary tonometer, which stands on the stage of the microscope at heart level. Light is thrown on the area

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5. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, *Am. J. Physiol.* **29**:335, 1912.

6. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Micro-capillary Tonometer, *Am. J. Physiol.* **52**: 136, 1920.

7. Weiss, E., and Dieter, W.: Die Strömung in den Kapillaren und ihre Beziehung zur Gefässfunktion, *Zentralbl. f. Herz. u. Gefässkrankh.* **12**:295, 1920.

to be observed by an electric bulb whose rays are focused by a condenser. A magnification of eighty diameters is employed. The capillaries are thus clearly brought into view and can be studied at leisure. Patients with a clinical capillary pulse are, however, difficult to study, because the finger moves with each pulse beat and the capillaries are thus thrown out of focus. This results in a very deceptive microscopic picture, for the finger movements rhythmically alter the focus of the microscopic field under observation. Thus with each pulse beat the capillaries become indistinct and may even disappear from view, to reappear immediately thereafter with their original clearness. This movement in and out of the focal field can readily be mistaken for a pulsation of the capillaries themselves. However, a close study, which, to be sure, is somewhat trying on the eyes, will convince the observer that the blood stream through the capillaries is at all times continuous and never pulsatile.

When the capillary blood stream is studied in this manner, it will be found that in most instances the flow is so rapid and steady that it can hardly be visualized. Each capillary is of a constant and uniform caliber. However, in individual capillaries the flow may be slow and almost halted at times but soon resumes its rapid streaming. Some individuals have a slower flow than others, and some a more rapid flow. With hypertension the velocity of the capillary blood appears to be increased; in arteriosclerosis it is decreased. But in spite of these individual variations, a capillary pulse was never observed. There was no intermittency of the circulation in the capillaries, nor was there any systolic lateral displacement of the capillaries.

Because of the fact that clinically the "capillary pulse" is usually observed best under slight pressure of the tissues, such pressure was exerted on the area studied by means of the Danzer-Hooker instrument. The pressure was elevated until the flow through the capillaries ceased, and was then gradually released to zero. At no pressure, not even with the first reappearance of the flow, was there the slightest departure from the normal continuous stream of blood. Both Weiss<sup>7</sup> and Jürgensen<sup>8</sup> have described pulsation of the capillaries observed through the microscope, but I am compelled to disagree with their findings. It is probable that the pulsation of the finger, discussed above, led them astray. I have seen this simulated capillary pulsation when the capillary flow was at a standstill because of the high pressure in the air chamber of the tonometer. Such an observation allows of no two interpretations and shows clearly with what care the studies must be made to avoid error.

The accompanying table gives a brief summary of the cases studied, together with the capillary pressure found in each instance. For reasons which will be detailed in a subsequent article, I have not averaged the pressures read in the different capillaries as advocated by Danzer and Hooker, but prefer to record them as individual readings. It seems quite certain that the variations of pressure observed in the same individual are of significance, and are not due to inaccuracy of measurement.

PATIENTS EXHIBITING CLINICAL CAPILLARY PULSE BUT NO MICROSCOPIC  
PULSATORY CAPILLARY FLOW

Case	Age	Sex	Diagnosis	Blood Pressure	Capillary Pressure, Mm. Hg	Room Temp., F.	Appearance of Capillaries
1	21	Male	Aortic insufficiency, rheumatic	140/ 50	10 10	..	Arrangement regular, some looped; subpapillary plexus visible
2	23	Male	Aortic insufficiency, rheumatic	115/ 60	20 20 18 25 22 23 26 15	78	Capillaries long, few loops
3	28	Male	Aortic insufficiency, rheumatic	140/ 50	20 18.5 10 13.5 17 10 11 8	65	Capillaries numerous, many rows, few tortuous; subpapillary plexus visible
4	18	Female	Aortic insufficiency, rheumatic	190/ 0	17 17.5 17	67.5	Capillaries numerous, not tortuous; subpapillary plexus visible
5	20	Male	Aortic insufficiency, mitral stenosis, rheumatic	150/ 20	8 5 7 12 12 7 10 16.5 15	70	Capillaries very long and numerous
6	12	Male	Aortic insufficiency, rheumatic	110/ 40	10 16 9 10.5	70	Capillaries very convoluted and irregular
7	8	Male	Aortic insufficiency, mitral stenosis, rheumatic	100/ 40	5 4 5 3	70	Capillaries normal
8	76	Male	Hypertension right hemiplegia	180/ 60	25 24 21 25 27 21 20	68	Capillaries long, convoluted; extensive subpapillary plexus
9	55	Male	Hypertension	205/110	17 31.5 12 19.5 23 22.5 18 18 17 26.5 34 38 29 28	65	Capillaries long, many convoluted; some giant capillaries
10	57	Female	Hypertension	145/ 75	25 20 27 33 18 14 30 31	75	Capillaries very convoluted; several rows; flow rapid
11	63	Female	Hypertension, diabetes	210/ 85	26 13 27 15 22 21 35 23 10 11.5 17 14.5	88	Longer and more tortuous than normal; subpapillary plexus prominent

Since, according to these observations the current views on the nature of the "capillary pulse" are erroneous, we must seek a new explanation of the phenomenon. At first thought it would seem that if the capillaries are not concerned in the production of this pulsation, it must be the minute arterioles in the subpapillary plexus of the skin which bring it about. This may be so in many instances, but Quinke's observations on the centripetal venous pulse, published in the same articles as those on the capillary pulse, suggest another possible interpretation. In some patients who exhibited clinical capillary pulsation he noted a post systolic centripetal pulsation of the veins on the dorsum of the hand. He believed it to be due to the propagation of the arterial pulse wave through the capillaries to the veins. In his second paper, however, he states that the capillary pulse is uncommonly found associated with the venous pulse. It is not quite clear how this comes about. Jürgensen<sup>8</sup> offers a possible explanation. He reviews the work of Hoyer,<sup>9</sup> Grosser<sup>10</sup> and Schumacher,<sup>11</sup> who demonstrated direct anastomoses between the arterioles and venules in the subpapillary plexuses, to explain some of the phenomena which he has observed in his studies of the capillaries. It is possible that the venous pulse, when it occurs, is caused by the transmission of the pulse wave through these subpapillary anastomoses, and that the clinical capillary pulse may be due to a pulsation of the subpapillary venules as well as arterioles. Additional evidence that the capillaries are not necessarily associated with the color of the skin is found in Weiss'<sup>12</sup> observation that on the skin of the cheek the capillaries are relatively scanty while the subpapillary venous plexuses are especially well developed, thus playing a dominant part in the production of the color of the skin of the cheek.

#### CONCLUSIONS

The so-called "capillary pulse" is not a manifestation of a pulsation of the capillaries, but is due to an exaggerated pulsation of the arterioles and possibly of the venules of the subpapillary plexus of the skin. In view of this fact it would be well to discard the term "capillary pulsation" and to speak of the systolic flushing of the skin.

8. Jürgensen, E.: Mikrokapillarbeobachtungen, *Deutsch. Arch. f. klin. Med.* **132**:204, 1920.

9. Hoyer, H.: Ueber unmittelbare Einmündung kleinster Arterien in Gefässe venösen Charakters, *Arch. f. mikroskop. Anat.* **13**:603, 1877.

10. Grosser, O.: Ueber arteriovenöse Anastomosen an den Extremitätenenden beim Menschen und den krallentragenden Säugethieren, *Arch. f. mikroskop. Anat.* **60**:191, 1902.

11. v. Schumacher, S.: Ueber das glomus coccygeum des Menschen, etc., *Arch. f. mikroskop. Anat.* **71**:58, 1908.

12. Weiss, E., and Holland, M.: Zur Morphologie und Topographie der Hautkapillaren, *Ztschr. f. exper. Path. u. Therap.* **22**:108, 1921.

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# The Capillary Blood Pressure in Arterial Hypertension

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NEW YORK





## THE CAPILLARY BLOOD PRESSURE IN ARTERIAL HYPERTENSION \*

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NEW YORK

Although the anatomy and physiology of the capillaries have been of interest to physiologists for many years and have been the subject of many investigations, their importance in the dynamics of the normal circulation and in the study of pathologic states is just beginning to be appreciated. The studies of Krogh<sup>1</sup> and Richards<sup>2</sup> on the response of the capillaries to the functional needs of the tissues; those of Dale<sup>3</sup> and Cannon<sup>4</sup> on the importance of the capillary mechanism in shock; the researches of Weiss<sup>5</sup> and his co-workers on the morphology of the capillaries and the character of the capillary flow in disease; and the studies of Kylin<sup>6</sup> and Danzer and Hooker<sup>7</sup> on the capillary blood pressure have within the last few years pointed out how essential a knowledge of the capillary function is to the clinician in his study of disease. The concept that the cardiovascular system is primarily adapted to maintain the blood flow in the capillaries, where the exchange of gases, food elements and waste between the tissues and the blood takes place, is a very fundamental one and one that cannot be overemphasized. It must further be recalled that the capillaries themselves play an active part in the maintenance of an adequate blood supply to the tissues, that they exhibit contractility and dilatability in response to nervous and metabolic stimuli and so assist in regulating the blood flow according to the needs of the tissues.<sup>8</sup>

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\* From the Medical Division of the Montefiore Hospital for Chronic Diseases.

1. Krogh, A.: The Supply of Oxygen of the Tissues and the Regulation of the Capillary Circulation, *J. Physiol.* **52**:457 (May) 1919; Studies on the Capillariomotor Mechanism. I. The Reaction to Stimuli and the Innervation of the Blood Vessels in the Tongue of the Frog, *J. Physiol.* **53**:399 (May) 1920.

2. Richards, A. N.: Kidney Function, *Am. J. M. Sc.* **163**:1, 1922.

3. Dale, H. H.: Capillary Poisons and Shock, *Bull. Johns Hopkins Hosp.* **31**:257, 1920.

4. Cannon, W. B.: A Consideration of the Nature of Wound Shock, *J. A. M. A.* **70**:611 (March 2) 1918.

5. Weiss, E., and Dieter, W.: Die Strömung in den Kapillaren und ihre Beziehung zur Gefässfunktion, *Zentralbl. f. Herz & Gefässkrankheiten* **12**:205, 1920.

6. Kylin, E.: Studien über das Verhalten des Kapillardruckes, insbesondere bei arteriellen Blutdrucksteigerungen, *Zentralbl. f. inn. Med.* **41**:368, 1920.

7. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, *Am. J. Physiol.* **52**:136 (May) 1920.

8. Hooker, D. R.: Evidence of Functional Activity on the Part of the Capillaries and Venules, *Physiol. Rev.* **1**:112 (Jan.) 1921.

In this study we have been particularly interested in the rôle which the capillaries play in the maintenance of the peripheral resistance to the blood stream, and consequently in the etiology of hypertensive states. The problem of hypertension and its relationship to kidney disease still remains unsolved in spite of innumerable searching studies that have been made. Opinion has veered from the extreme view that hypertension is always a result of kidney disease to the opposite extreme that all kidney disease is secondary to hypertension. Both schools still have their advocates. From the maze of facts and theories that have surrounded the subject, one thesis may be granted as established—that the syndrome of hyperpiesia or essential hypertension may exist without any evidence of nephritis. Whether “nephritic hypertension” is a late stage of this or quite a different syndrome is unknown. Blood pressure studies have been singularly unilluminating in clearing up the matter. We have learned to appreciate that brachial blood pressure readings are very variable and that in many instances they depend on the degree of contraction of the arterioles. That the capillaries themselves may be concerned in the maintenance of this pressure was first brought out forcibly by Dale and Cannon, who showed that a paralytic dilatation of the capillaries may cause a great fall in blood pressure, even when the arterioles are contracted. The reverse side of the picture, namely, that the capillaries may themselves be a factor in the maintenance of high arterial pressures, is suggested by some of the studies of Kylin and of Weiss.

Kylin,<sup>6</sup> using an instrument something like Danzer and Hooker's, has made some very interesting observations on the capillary blood pressure in hypertension and nephritis. His observations are open to question because he used the cessation of the capillary blood flow as the criterion by which he measured the capillary pressure and also because his figures for normal readings are uniformly low—about 10 mm. Hg. In glomerular nephritis he found the capillary pressure abnormally high in 100 cases investigated, but in benign nephrosclerosis with hypertension it was always normal. He studied twenty scarlet fever convalescents daily and found in some a marked increase in capillary pressure. In three of these patients a typical glomerular nephritis developed with albumin, casts and red cells in the urine a few days after the capillary pressure had risen. The nephritis set in when the capillary pressure had reached about 23 mm. of mercury. The highest capillary pressure obtained ranged from 40 to 55 mm. of mercury. In a more recent article,<sup>9</sup> written in English, he summarizes the results of

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9. Kylin, E.: Brief Notes on Hypertonia and Kidney Disease, *Acta Med. Scandin.* **55**:368, 1921.

his studies as follows: There are two types of hypertension. The nephrosclerotic hypertension is an arterial, the glomerulonephritic, a capillary hypertension. In the first form the brachial blood pressure is much more labile than in the latter. The hypertension is not the result of the kidney disease, but the glomerulonephritis is a manifestation of a diffuse capillary injury caused by the toxins of certain acute infectious diseases. Some of Weiss'<sup>10</sup> observations seem to confirm these views. He noted an increase in the number and a change in the appearance of the capillaries of the nail-bed in acute, as well as in chronic nephritis. They were longer and more convoluted than normal.<sup>11</sup> These observations were confirmed by Thaller and Draga<sup>12</sup> but disputed by Schur.<sup>13</sup>

With these studies in mind we studied a series of patients with hypertension in the wards of the Montefiore Hospital.

We employed the microcapillary tonometer described by Danzer and Hooker<sup>7</sup> for our determination of the capillary blood pressure. It is the most satisfactory instrument that has been devised for this purpose. In principle it resembles the instrument which Roy and Brown<sup>14</sup> devised in their studies on the capillaries of the frog. Lombard's<sup>15</sup> observation that the human capillaries could be visualized by observing the skin through a microscope after a drop of oil or glycerin had been applied to it was the next step in the development of the technic. Kraus<sup>16</sup> followed this lead and studied the pressure of human capillaries, using a magnification of 10 diameters. It remained for Danzer and Hooker to develop a practical, convenient technic, and to introduce the principle that the cessation of the blood flow in the capillaries, rather than the disappearance of the capillaries marks the proper pressure at which the reading should be taken.<sup>17</sup>

10. Weiss, E.: Beobachtung und microphotographische Darstellung der Hautkapillaren am lebenden Menschen, *Deutsch. Arch. f. klin. Med.* **119**: Heft 1 and 2, 1916.

11. Weiss, E.: Das Verhalten der Hautkapillaren bei akuter Nephritis, *München. med. Wchnschr.* **63**:925, 1916.

12. Thaller, L, and v. Draga, E.: Zur diagnostischen Verwertbarkeit der mikroskopischen Hautkapillarenuntersuchung am lebenden Menschen, *Wien. klin. Woch.* **30**: No. 22, 1917.

13. Schur, H.: Mikroskopische Hautstudien am lebenden, *Wien. klin. Woch.* **32**:1201, 1919.

14. Roy, C. S., and Brown, J. G.: The Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, *J. Physiol.* **2**:323, 1879.

15. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, *Am. J. Physiol.* **29**:335, 1912.

16. Krauss: Der Kapillardruck, *Sammlung klin. Vorträge Inn. Med.* No. 237-239, 315, 1914.

17. For a critical survey of methods to determine capillary pressure see Friedenthal, *Ztschr. f. exper. Path. & Therap.* **19**:2, 1917.

TABLE 1.—RESULTS OF EXAMINATION OF TWENTY-THREE CASES

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
1. (A. G.)	M	55	Hypertension, chronic lead poisoning?	No hypertrophy of heart; aortic second sound accentuated; thickening and tortuosity of temporals; slight of radials	1.023 Alk. No albumin No casts	39.0	Urea N.....10.5 Uric A.....1.9 Sugar......97	130/90-95	R-4 27.0 25.0 30.0 23.5 31.0 27.0 24.0 29.0 40.0 L-3 21.5 23.0 30.0 L-4 33.0 35.0 41.0 34.0 L-5 30.0	More looping of the venous arms than normal; many small fine capillaries with one small fine convolution present
2. (M. G.)	M	58	Hypertension, chronic nephritis	Cardiac hypertrophy; 2 attacks of hemiplegia; headaches, shortness of breath, swelling of eyelids; Wassermann negative	Alb. ++ Many casts	32.0 36.0	Urea N.....15.0 Uric A...... 3.1	230/128  235/120	30.0 27.0 27.0 30.0 43.0 43.0 46.0 36.0 37.0 33.0 32.0 L-3 38.0 45.0 L-5 44.0 25.0 27.0 33.0 36.0	Capillaries long, few looped
3. (S. W.)	M	50	Hypertension, chronic nephritis, diabetes	Cardiac hypertrophy; albuminuric retinitis, shortness of breath, swelling of feet; left chest tapped a number of times, bloody fluid withdrawn	Marked trace of albumin Many granular casts	40.0 32.5	Urea N. 5/25/21.....17.5 8/21/21.....27.4 10/5/21.....25.4 Uric A...... 2.5	244/150	35.0 40.0 53.0 49.0 R-3 85.0 60.0 50.0 R-5 41.0 43.0	Capillaries irregularly convoluted; subcapillary plexus seen

4. (M. L.)	F	53	Hypertension, chronic nephritis, arteriosclerosis	Cardiac right hypertrophy; thickened tortuous vessels; Wassermann negative	Alb. trace Granular casts	20.0	Urea N.....13.5 Uric A..... 13 Creat..... 4.2	216/120	L-3 40.0 30.0 38.0 31.0 33.0 38.5 30.0 32.0 49.0 46.0 37.0 R-3 14.0 11.0 14.0 12.0 13.0 39.0 83.0 90.0 R-2 65.0 47.0	Left; capillaries very long, in several layers, not tortuous. Right; (hemiplegic), capillaries long, wider, some wound
5 (Ph. D.)	M	61	Hypertension, chronic nephritis, arteriosclerosis, emphysema	Cardiac hypertrophy, adv. thickening and tortuosity of vessels; Wassermann negative; high blood pressure since October, 1918	Alb. and casts	18.0	Urea N.....11.4 Uric A..... 5.1	212 110	R-3 40.0 46.5 45.0 37.5 54.5 52.0 36.0 R-4 32.5 R-5 38.0 L-3 36.5 39.0 41.0 31.0 39.0 35.0 L-4 39.0 39.5 40.0 L-2 50.0 47.0 L-5 45.0	Very many convoluted capillaries  Long narrow capillaries Capillaries looped, longer than normal, (hemiplegic side)  Very many capillaries, looped  Capillaries are long, parallel, regular, venous end thick, many subcapillary plexuses (venous)  Very long, straight and looped capillaries with engorged venous ends
6. (B. H.)	F	52	Hypertension, chronic nephritis and auricular fibrillation	Cardiac hypertrophy; attacks of decomposition	Alb. and casts	41.0	Urea N.....12.6 Uric A..... 2.1 Sugar.....119	228/110	L-3 66.0 70.0 L-5 70.0 R-4 63.0 48.0	Capillaries are long, parallel, regular, venous end thick, many subcapillary plexuses (venous)
16. (M. L.)	M	39	Hypertension, chronic nephritis	Heart normal; Wassermann negative; high blood pressure since April, 1921	1.012-1.027 Occasional hyaline casts	45.0	Urea N.....23.8 Uric A..... 1.95	216/120	74.0 45.0 60.0 22.0 60.0	

R, right hand; L, left hand; figures 2, 3, etc. indicate the finger of the hand. Thus, R-4 means the fourth finger of the right hand.

TABLE 1.—RESULTS OF EXAMINATION OF TWENTY-THREE CASES—(Continued)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
17. (C. G.)	F	59	Hypertension, chronic nephritis	Vertigo, dizziness, headaches past six years; slight cardiac hypertrophy; slight accentuated second sound and pulmonary second sound; blood pressure 235/140	1.010 (24 hr.) 1.011 Alb. 0	...	N.P.N.....45.5 Urea N.....39.0 Uric A..... 2.8 Creat..... 1.37	196/120	35.0 45.0 26.0 65.0 60.0 65.0 56.0 42.0 52.0 44.0	Capillaries numerous and tortuous
21. (F. W.)	M	60	Arteriosclerosis extensive, with calcification of small arteries and gangrene of leg	Diabetes (?) and dizziness; cardiac hypertrophy; amputation of left leg one year ago for gangrene; cerebral hemorrhage with high blood pressure four years ago	1.005-1.018 Alb. trace No casts Many W.B.C.	26.5	Urea N..... 9.1 Uric A..... 3.4 Creat..... 1.5 Sugar.....127.0	164/90	L-4 21.0 35.0 27.0 27.0 25.0 L-5 41.0 39.0 33.0 31.5 29.0 L-2 49.0 40.0 40.0 22.0 R-4 26.5 26.5 26.5 R-2 42.0 36.5 36.5	Capillaries long, looped, irregular, many layers, subcapillary, very irregular architecture; streaming at 0 mm.; venous end thick
7. (A. G.)	M	59	Hypertension, diabetes mellitus	Cardiac hypertrophy (slight); mild diabetes; with few symptoms; Wassermann negative	1.015-20 Alb. neg. Sugar trace No casts	45	Urea N..... 18.9 Uric A.....2.5 Sugar.....238	174/110	L-5 15.0 16.0 18.0 14.0 14.0 L-4 18.0 21.0 17.5 L-2 16.5 16.5 17.5 L-3 17.5 18.5 14.0 17.0	Capillaries increased, no straight loops, curved but not entwined; venous ends somewhat engorged Very greatly elongated and curved; engorged venous ends Many elongated tortuous capillaries Same

8. (J. S.)	M	44	Hypertension, arteriosclerosis, emphysema, chronic valvular disease, mitral stenosis	Cardiac hypertrophy; aortic second sound ++; slight sclerosis, temporal artery; clubbed fingers; Wassermann negative	1,014-20 Alb. 0 to V. F. T. No casts	30	Urea N.....15.4 Uric A.....1.7	164/94	B-5 15.0 12.0 14.0 16.5 B-4 22.0 27.0 19.0 20.0 22.0 13.0 10.0	Tortuous and elongated  Massive capillaries, some tremendously engorged  Many large and small capillaries, normal in appearance  Very many capillaries to field
9. (J. R.)	F	69	Hypertension, general arteriosclerosis, auricular fibrillation	No cardiac hypertrophy; amputated left foot for gangrene; blood pressure 170 on admission	No albumin or casts	4 32.5	Urea N.....14.7 Uric A.....1.3 Sugar......62	145/90	1.3 4.0 2.0 6.0	Very many capillaries, most in long loops, few with convolutions; streaming at 0; subcapillary plexus visible
10. (P. K.)	F	60	Hypertension, arteriosclerosis	Cardiac hypertrophy; slight thickening of radials; left hemiplegia three years ago; Wassermann negative	Alb. ++ R. B. C. No casts (cystitis)	9/9/21 12.5 10-22-21 20.0	Urea N.....11.9	175/85	R-4 5.0 R-3 7.0	Capillaries looped, irregularly arranged, Hemiplegic hand not examined
11. (B. S.)	F	55	Hypertension, arteriosclerosis	Cardiac hypertrophy; left hemiplegia three years ago; Wassermann negative; blood pressure 250/120 One year ago; second stroke with death; necropsy	1,010-1,016 Alb., faint trace No casts	25.0	Urea N.....27.3	180/95	R-3 15.0 17.0 15.0 12.0 R-4 9.0 7.0 R-2 11.5 7.5 9/16-21 20.6 1.5 30.0 17.0 15.0 14.0 L-2 73.0 68.0 66.0 62.0 56.0 47.0 37.0 6.0 34.0	Capillaries long, irregular, tortuous; "granular" streaming at 0; extensive subcapillary plexus with capillaries running into it  Almost normal looking  Extremely convoluted; great number flowing at 75; flow visible at 0; streaming both "granular" and rapid
12. (P. F.)	M	66	Hypertension, arteriosclerosis, emphysema	Slight cardiac hypertrophy; sclerosed arteries; clubbed fingers; Wassermann ±	1,011-22 Alb. ++ Sugar ++ No casts	17.5	Urea N.....10.8 Uric A.....2.8 Sugar.....101.0	180/100		

TABLE 1.—RESULTS OF EXAMINATION OF TWENTY-THREE CASES—(Continued)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
12. (P. F.) (Continued)	..	..	.....	.....	.....	.....	.....	158/85	10/10/21: L-2 16.0 14.0 10.0 L-5 13.0 11.0 10.0 20.0 16.0 11.0 R-4 20.0 R-5 6.0 R-2 12.0	Some capillaries very large; many convoluted many times; irregular in arrangement; subpapillary plexus visible
13. (B. P.)	F	63	Hypertension, emphysema, diabetes mellitus	Moderately enlarged heart; aortic second sound ++; microscopic cap. pulse; both legs amputated for diabetic gangrene 5 years ago; (X-ray calcified arteries); Heberden's nodes on all fingers; blood pressure, 180/146 in 1919, 190/80 in 1921; Wassermann negative	1011-1022 Alb. ++ Sugar ++ Hyalin and granular casts	7.5	3/3/21: Urea N.....15.7 Sugar.....130  10/19/21: Urea N.....36.6 Sugar.....132.0  12/7/21: Urea N.....92.4 Sugar.....122.0	198/80  210/85	R-3 26.0 27.0 25.0 32.0  R-4 13.0 15.0 R-3 21.0 R-2 23.0 21.5 10.0 14.0 11.0 L-4 14.5 11.5 L-3 17.0	Very many small fine capillaries  Longer and more tortuous than normal  Very long capillaries; subpapillary plexus visible
14. (M. G.)	F	47	Hypertension, chronic nephritis (?)	Cardiac hypertrophy; aortic second sound greater than pulmonic second sound; systolic at apex and base; blood pressure 220/120; Wassermann negative	10/10/13 Alb. ++	63 1 hr. (intravenous)	N.P.N.....38.6 Urea N.....29.4 Uric A.....3.6	204/140	L-3 11.0 6.0 19.0 7.0 11.0 23.0 25.0 13.0 L-2 17.0 23.0 21.0 22.0 13.0 16.5 L-4 28.5	Long, somewhat convoluted Capillaries very long, extremely looped  Very long, looped  Very long and convoluted, few loops



15. (N. D.)	F	56	Hypertension	Cardiac hypertrophy; aortic second sound ++ greater than pulmonic second sound; blood pressure 235/120 to 190/100; normal arteries; normal eye grounds	1.01.20 Alb 0 to V. F. T. No casts Sugar +	73	Urea N.....2.7 Creat.....0.0 Sugar......94	285/100	R-2 29.0 L-2 29.0 L-3 10.0 R-3 30.0 R-4 22.0 R-5 12.0 R-6 6.0 R-7 13.0 R-8 13.0 R-9 13.0 R-10 11.0 R-11 10.0 R-12 12.0 R-13 7.5 R-14 7.0 R-15 7.0 R-16 8.0 R-17 7.0	Massive capillaries with many convolutions Very wide and long Very long, no loops Capillaries numerous, long; several layers deep, moderately tortuous
16. (S. S.)	M	62	Hypertension, asthma, chronic bronchitis, myocardial degeneration	"Asthmatic attacks"; no enlargement of heart; headaches; secondary anemia	1.01.14 No alb. No casts	47.5	Urea N.....19.4 Uric A.....3.9	174 72	R-4 11.0 R-5 4.0	Capillaries extremely long; crowded together with many convolutions; granular streaming in most at 0; great number of anastomoses
19. (F. G.)	F	48	Hypertension, chronic nephritis, uremia	Persistent vomiting; loss of weight and strength; headaches; cardiac hypertrophy; secondary anemia; Wassermann +	1.07.1.030 Alb. marked trace Rare gr. casts W. B. C. Some R. B. C.	6	Urea N.....10.26 Uric A.....156.0 Creat.....94 Creat.....7.4 Urea N.....10.31 Uric A.....112.0 Uric A.....11.6 Urea N.....11.11 Urea N.....140.0 Uric A.....7.3	195/104	R-3 5.0 R-2 10.0	Capillaries very long, no loops; flowing at 0 with granular streaming
20. (S. S.)	M	55	Hypertension, cardiac hypertrophy, emphysema; chronic nephritis	Edema of legs, dyspnea, abdominal distention; Wassermann negative	1.04.1.031 Alb. trace Hyalin and granular casts	40	Urea N.....23.0	225/100	9/19/21: 1.3 31.5 17.0 19.5 12.0 23.0 22.5 R-4 18.0	Capillaries long, many with one or more loops, quite irregular; some capillaries very thick

TABLE 1.—RESULTS OF EXAMINATION OF TWENTY-THREE CASES—(Continued)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance		
20. (S. S.) (Continued)	..	..	.....	.....	.....	.....	.....	.....	18.0 15.5 19.5 22.5 R-5 17.0 26.5 23.5 13.0 R-2 38.0 25.0 26.0 10/13/21: R-4 28.5 21.0 25.0 23.0 L-3 26.0 29.0 25.0 L-4 34.0 27.0 21.0 38.0	.....	.....	.....
22. (G. F.)	M	68	Hypertension, chronic nephritis, emphysema	Cardiac hypertrophy; aortic second sound +; old left hemiplegia; blood pressure 200/140 to 210/120; no cardiac symptoms	1.016-1.017 Alb. trace Few hyaline casts	Less than 5	Urea N.....17.6 Uric A..... 1.6	210/120	R-3 26.0 20.0 L-4 11.0 4.0 0.0	Capillaries long, many convoluted; no flow at 0 min. in many capillaries; many rows of capillaries visible		
23. (B. J.)	F	45	Hypertension, general arteriosclerosis, chronic nephritis	Left hemiplegia three years; headaches; cardiac hypertrophy; aortic second sound +; old hemorrhages in fundi	1.008 Alb. ++ Few granular casts	21	Urea N.....14.1	238/138	R-4 24.0 24.0 19.0 R-5 23.5 16.5 20.0 19.0	Capillaries very long and thin; very many to field; no convolutions; subcapillary plexus visible		

We followed the method of Danzer and Hooker, as outlined in their article. All readings were taken with the hand at heart level and the patient in a sitting posture, at a room temperature of 20-25 C. After the first few observations, we did not scrub the skin of the finger before making our readings, for we found it unnecessary and did not wish to introduce a possible complicating factor. Leonard Hill<sup>18</sup> has questioned the accuracy of this method. He states that the true measure of the blood pressure in the capillaries is that pressure which, when applied, will momentarily check the flow of blood in the capillaries, and that the pressure which will completely check the flow is equal to the pressure in the arterioles which supply the area compressed, because of the backing up of pressure in the occluded vessel. This is undoubtedly true. However, we have followed Danzer and Hooker's procedure of taking the reading as one does a blood pressure reading, i. e., noting the point at which the capillary flow returns as the pressure which has stopped the flow is released. With the drop in pressure, the blood first flows sluggishly through the capillaries but suddenly quickens to a rapid stream. This we have taken as the capillary pressure, and to this Hill's objections do not apply. Hill's second objection is that with this method, the pressure factor dependent on the resistance of the skin to compression is not excluded. As a matter of fact, by a method of his own he obtains very low readings for capillary pressures, from 2 to 5 cm. of water. Our observations seem to indicate that the resistance of the tissues does not appreciably modify the reading. We have examined many patients who exhibited marked atrophy of the skin in the area studied, as well as many whose skin was normal and others with quite a horny epidermis. The readings obtained did not vary according to the condition of the skin. Moreover in several patients with vasomotor disorders of the extremities we obtained a normal reading—about 20 mm. mercury on one day, and a very low reading—from 2 to 3 mm. mercury on another day. The latter reading is so low as to practically exclude the resistance of the skin as a factor.

It is well known that venous stasis will induce an elevation of the capillary pressure. We were careful, therefore, to exclude this factor in the cases studied. The observations detailed in the following table were made on patients whose systolic pressure was 180 mm. Hg. or over, selected at random in the wards of the Montefiore Hospital. For five of the cases we are indebted to the courtesy of Dr. H. J. Wiener, who permitted us to examine them in his Metabolism Division of the Vanderbilt Clinic.

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18. Hill, L.: The Capillary Blood Pressure, *J. Physiol.* **54**:xxiv, 1920, *ibid.* **54**:xciii., 1921; Hill, L., and McQueen, J. M.: The Measurement of the Capillary Blood Pressure in Man, *Brit. J. Exper. Path.* **2**:1, 1921.

Danzer and Hooker determined that the normal capillary pressure ranged from 18 to 22 mm. of mercury. They found that in any individual most of the readings on different capillaries varied from 6 to 7 mm. of mercury, although in many capillaries the difference was greater. They, however, discarded the very high and the very low readings and took as the capillary blood pressure the average of those which did not exceed this variability. We, too, as is apparent from

TABLE 2.—SHOWING THE DISTRIBUTION OF THE READINGS OF CAPILLARY PRESSURE \*

Case	Mm. Mercury								
	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Patients With Hypertension:									
1.....	..	..	11	5	1	..	..	..	..
2.....	..	..	7	6	5	..	..	..	..
3.....	..	..	..	2	4	2	..	..	1
4.....	..	6	1	9	3	..	1	..	2
5.....	..	..	..	13	6	3	..	..	..
6.....	..	..	..	..	1	..	4	..	..
16.....	..	..	2	..	1	2	..	..	..
17.....	..	..	1	1	3	3	2	..	..
21.....	..	..	..	..	..	..	..	..	..
7.....	..	23	4	..	..	..	..	..	..
8.....	5	..	..	..	..	..	..	..	..
9.....	3	..	..	..	..	..	..	..	..
10.....	2	..	..	..	..	..	..	..	..
11.....	3	5	..	..	..	..	..	..	..
12a.....	4	2	1	1	1	4	14	..	..
12b.....	3	9	..	..	..	..	..	..	..
13.....	1	7	6	1	..	..	..	..	..
14.....	6	15	13	2	..	..	..	..	..
15.....	5	2	..	..	..	..	..	..	..
18.....	1	1	..	..	..	..	..	..	..
19.....	3	..	..	..	..	..	..	..	..
20a.....	..	9	7	2	..	..	..	..	..
20b.....	..	..	9	2	..	..	..	..	..
22.....	2	2	1	..	..	..	..	..	..
23.....	..	4	3	..	..	..	..	..	..
Patients With Normal Blood Pressure:									
24.....	..	7	12	1	1	..	..	..	..
25.....	..	21	20	..	..	..	..	..	..
26.....	..	..	18	1	..	..	..	..	..
27.....	3	11	9	3	1	..	..	..	..
28.....	11	..	..	..	..	..	..	..	..
29.....	1	8	4	..	..	..	..	..	..
30.....	3	11	1	..	..	..	..	..	..
31.....	..	3	..	..	..	..	..	..	..
32.....	6	15	5	3	..	..	..	..	..
33.....	3	12	5	..	..	..	..	..	..
34.....	..	..	3	..	..	..	..	..	..
35.....	..	..	2	2	1	..	..	..	..

\* Cases in which only very few readings are recorded are ones in which all of the capillaries in the microscopic field exhibited a reappearance of the blood flow at the same pressure. Early in the work the number of capillaries observed were not counted.

Table 1, encountered wide differences between the pressure readings in different capillaries of the same individual. This variability is so constant in most cases that we feel it cannot be ignored. It has long been known that there is a great variation in the degree of filling of different capillaries and in the rate of their blood flow. Roy and Brown drew attention to this in 1879 and many others have subsequently noted the same phenomenon. It remained for Krogh to point out the relationship of this variability of flow to the functional needs of the

tissues. With the inconstancy of flow there must be a corresponding fluctuation of the capillary pressure. Thus the variations in the readings which we observe are of real significance and should be recorded. We deem it wisest to record all of the observations. Because of the wide range of variability and the relatively small number of readings, an average would be deceptive. It is possible that the degree of variability of the readings in different individuals may have some clinical significance. That it is not due to errors of measurements is shown by the fact that successive readings on one capillary taken at the same sitting are usually quite constant.

It has been suggested that high readings are due to the fact that the capillaries on which such pressures are observed are seated more deeply in the tissues, or that some anatomic peculiarity is the determining factor. The following facts show that this does not usually obtain. By careful focussing of the microscope one can show that the capillaries giving high readings are often superficial. The size of the capillary bears no relationship to the pressure observed therein. Moreover, if the same group of capillaries is kept under observation for a period of time, or is studied on different days, marked variations in their pressure are observed. For instance, in Case 6 a group of four capillaries of varying shapes and sizes gave the following successive readings, the figures for all four capillaries at any one time being the same—45, 38, 52. Four days later the readings were 48, 49, 49, 55. On both days during the period of observation one of the four capillaries disappeared from view for several minutes at a time. On such occasions we were able to make it reappear by raising the pressure to 90 or 100 and quickly releasing it several times in succession. This acts, we believe, as a mechanical stimulus to the arterioles, capillaries and venules. In another patient (Case 26) the following note was made:

While the pressure in most of the capillaries in the microscopic field was 28, in one capillary there was but the slightest streaming of blood at 0. The pressure was raised to 90 and quickly released. Thereupon the microscopic field became markedly hyperemic and the pressure in most of the capillaries was 25. In the capillary in which the reading had been 0, the pressure now was 12.

We think that at times unlike pressures in different groups of capillaries are due to the fact that the arterioles supplying the groups exhibit different pressures or degrees of contraction. Case 25 may be cited as an example. Observations made on the fourth finger of the left hand passing from the left to the right side of the nail-bed, so that the first and last readings were made on capillaries separated by a distance of one centimeter, were as follows:

Left 8, 8.5, 10, 15, 20 Right  
and again Left 10, 10, 14, 15.5, 17, 20 Right

It is clear from this discussion that the capillary pressure in the same and different vessels may vary from physiologic as well as from anatomic causes.

It is difficult to draw any final conclusions from a study of the tables. The cases fall into two groups—those with high capillary pressure and those with a low or normal capillary pressure. It is impossible to classify the patients clinically. Neither the history, the physical examination, nor the study of kidney function reveals any differential features. Similar urinary findings are common to both groups; in both we find low as well as normal phenolsulphonephthalein excretion. There is no difference in the pulse pressures in the two series. While it is true that on the average patients with a high capillary pressure exhibit a high diastolic blood pressure, there are sufficient exceptions to this rule to invalidate any supposition of a causal relationship between the two.

On further reflection these apparently vicarious figures find some theoretical justification. If Kylin's division of hypertensive states is a correct one, it may well be that those of our patients who showed kidney involvement with a low capillary pressure did not fall within the group exhibiting glomerulonephritis and general capillary disease. As a matter of fact necropsies in two of our cases support this belief. The following extracts from the autopsy protocols of Cases 11 and 19 give no evidence of a diffuse glomerulonephritis:

#### REPORT OF NECROPSY FINDINGS

CASE 11.—Right kidney weighs 120 gm.; left, 80 gm. Capsule markedly adherent. Scattered large arteriosclerotic scars. On section the cortex varies in thickness, striations irregular, vessels prominent.

Microscopic examination reveals scarring with thickening and obliteration of the vessels in the depressed areas. Slight fibrosis of the glomeruli with some thickening of Bowman's capsule. In the scarred areas the glomeruli are fibrosed.

There is marked arteriosclerosis of the aorta, of the cerebral and coronary arteries. In the posterior wall of the left ventricle there is a large white scar. There is a large cystic area in the right occipitoparietal region, and a hemorrhage in the left internal capsule.

CASE 19.—Each kidney weighs 50 gm. They are firmer than normal. Capsule adherent, leaving on removal a finely granular surface. The cut surface is pale and granular. The cortex is from 2 to 3 mm. in diameter. Striations are absent. Small vessels are prominent.

Microscopic examination shows a complete loss of normal architecture. Marked sclerosis of the larger vessels. Tubules are arranged in irregular groups and are dilated. Their cells are low, cuboidal, and the lumen is filled with exudate. There is a great deal of connective tissue with round cell infiltration. Most of the glomeruli have undergone a fibrous or hyaline change. A few still have a normal appearance, but even in these Bowman's capsule is much thickened.

Diagnosis: Primary contracted kidney.

When we recall that experienced clinicians have recognized the impossibility of diagnosing the anatomic lesion in the kidney from the clinical picture, particularly in chronic nephritis, we are in a position to understand why, in the cases we studied, we have been unable to predict which cases will exhibit a high capillary pressure as one of the manifestations of a glomerulonephritis. If our postulates hold true, however, and for confirmation we must await the postmortem examinations on appropriate cases, the estimation of the capillary pressure may prove an important aid in the differential diagnosis of glomerulonephritis, from other types of kidney disease. It is not, however, of value in the differentiation of nephritic from essential hypertension.

Another question which remains unsolved is whether the capillary hypertension contributes to the general arterial hypertension, or whether it is a concomitant phenomenon. It is well known that when, in patients with hypertension, particularly, serial blood pressure readings are taken, the final reading will often be considerably lower than the first one. Table 3 presents such a series of readings on the two groups of patients:

TABLE 3.

High Capillary Pressure	Blood Pressure in Mm. Hg					Length of Observation, Min.	Drop in Systolic Blood Pressure, Mm. Hg
Case 2	240/120	230/110	220/100	206/100	206/100	5	34
Case 3	206/120	204/120	200/120	202/120	200/110	10	6
Case 5	250/140	240/150	228/125	214/125	212/122	12	38
Low Capillary Pressure							
Case 7	180/110	184/106	184/110	180/110	180/110	10	0
Case 12	184/102	176/96	174/96	180/94	178/96	12	6
Case 8							
10/ 8/21	186/ 90	174/ 90	170/ 80	168/ 80	160/ 90	10	26
10/10/21	152/ 82	160/ 90	154/ 86	158/ 88	156/ 88	10	4
12/ 1/21	184/100	180/ 90	166/ 90	176/ 96	174/ 94	10	10
12/ 6/21	174/ 96	172/ 94	170/ 90	174/ 90	172/ 90	10	2

It is apparent that the blood pressure is equally unstable in both groups. Were the high capillary pressure a cause for the sustained hypertension, one might imagine that in such cases the blood pressure readings would be more constant.

Furthermore, were the connection a close one, one would expect the blood pressure to vary, *pari passu*, with the capillary pressure. We have observed this only in Case 12, where readings taken on different days at different levels of blood pressure revealed parallel changes in the capillary pressure. We must dispute the statement of Secher<sup>19</sup> that the capillary pressure, as a rule, follows the blood pressure. He cites one case in which wide fluctuations of the blood pressure were accompanied by parallel changes in the capillary pressure.

19. Secher, K.: Kliniske Kapillaerundersøgelser, Ugeskrift f. Læger **83**:800, 1921.

The mechanism of a low capillary pressure is easily explained. A constriction of any blood vessel will be followed by a rise of pressure central to the constriction, and by a fall of pressure peripheral thereto. In hypertension, due to a contraction or a diminution of the lumen of the arterioles, the capillary pressure will be low. Thus it would seem that in most of our cases of hypertension there is a narrowing of the arterioles. A high capillary pressure will follow a dilatation of the arterioles or a constriction of the venules, or a high venous pressure due to stasis. It is not clear how disease of the capillaries themselves would lead to a high capillary pressure, particularly when we recall that arteriosclerosis of itself does not lead to a high arterial pressure. This is the weak point in Kylin's theory. It is conceivable that a lesion of the venous loop of the capillary might raise the pressure in the arterial loop, or that a stiffening of the endothelial tube due to disease might increase the pressure needed to check the blood flow in the capillaries.

That the appearance of the capillaries in our cases does not correspond to the accepted normal is evident from the table. We are not ready, however, to subscribe to Weiss' positive views as to the significance of these morphologic changes. We believe that the normal has not yet been sufficiently established. We have observed in normal individuals capillary pictures that correspond to descriptions of the capillaries characteristic of nephritis and arteriosclerosis. In general, it may be said, however, that the capillaries when diseased behave as do the arteries. They become long and, as a consequence, tortuous. This may be due to an organic change in the capillary or it may be as Lapinsky<sup>20</sup> pointed out, due to loss of tone following injury to the nerve supplying the area in question.

#### CONCLUSIONS

1. In patients with normal blood pressures the blood pressure in the capillaries of the fingers rarely exceeds 30 mm. of mercury.
2. Patients with hypertension fall within two groups that cannot be differentiated clinically. In the first group the capillary pressure ranges between 21 and 70 mm. of mercury, rarely higher and only very exceptionally lower. Most of the readings fall between 30 and 60. In the second group the capillary pressure falls within the range of normal, with a tendency to be low rather than high.
3. It is possible that patients who exhibit high capillary pressures are suffering from a general capillary disease with a glomerulonephritis as one of the manifestations. If this view is confirmed, the estimation

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20. Lapinsky, M.: Studien über die lokale Blutzirkulation im Bereiche gelähmter Nerven, *Arch. f. Anat. & Physiol. (Physiol. Abtheil.)* 477, 1899. Supplement.



of the capillary pressure may prove an important aid in the differential diagnosis of glomerulonephritis from other forms of kidney disease.

4. In essential hypertension the capillary pressure is low.

5. In any given individual varying pressures are usually observed in different capillaries. In patients with a normal capillary pressure the difference between the high and low readings is on the average 18 mm. Hg. In patients with a high capillary pressure this difference is on the average 36.6 mm. Hg. Thus the variability of the capillary pressure is greater in patients with high readings.

6. The variability of the capillary pressure depends on physiologic as well as on anatomic moments.

7. Mechanical stimulation of the capillaries will alter the blood flow, as well as the blood pressure within the capillaries.

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# RESUSCITATION BY THE INTRA-CARDIAC INJECTION OF EPINEPHRIN \*

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Instances of recovery, after failure of the heart action, by the injection of epinephrin into the heart are sufficiently rare to justify the report of a case in which this occurred:

## REPORT OF CASE

S. K., a man, aged 73, with generalized arteriosclerosis, was admitted to the hospital, June 26, 1921, complaining of severe pain in the right leg due to trophic changes. The patient was in fairly good condition for his age, although there was marked emphysema of the lungs, and emaciation. The heart sounds were distant and of poor quality. The arteries of the extremities were tortuous and much thickened. There was marked atrophy of the muscles of the right lower extremity. Neither the dorsalis pedis nor the popliteal arteries could be felt. The Wassermann blood test was negative. The urine contained a trace of albumin, but no casts. The blood analysis revealed the urea nitrogen as 12.2. The systolic blood pressure was 176, diastolic 80.

The pain continued to be very severe, and, September 20, amputation of the affected extremity under spinal anesthesia was attempted. The patient was placed in a sitting position on the operating table, and after 10 c.c. of spinal fluid had been withdrawn, 10 c.c. of 1 per cent. solution of procain was injected into the spinal canal, followed almost immediately by drowsiness, cyanosis and shallow respiration. The heart action remained good for about five minutes, when the patient became unconscious, respiration ceased, and the pulse and the heart sounds could not be detected. Artificial respiration was begun and various cardiac stimulants, including caffein, camphor and epinephrin, were given hypodermically, but without effect; the breathing had ceased and the heart action seemed to have ceased. Twenty minims (1.2 c.c.) of epinephrin, full strength, was then injected into the left auricle by puncture of the chest wall between the left third and fourth ribs, the position in the cavity of the heart having been determined by aspiration of blood. There was immediate reappearance of the radial pulse and of feeble respiratory efforts. This was followed by the return of the heart sounds. The cyanosis was gradually replaced by nor-

\* From the Surgical Service, Montefiore Hospital.

mal color, and within a few minutes, respiration became regular, the heart action good, and consciousness was restored. After this the patient made an uneventful recovery from his symptoms.

As the pain continued for a number of months, the extremity was finally amputated above the knee, under gas and oxygen anesthesia. Recovery was prompt and the patient was discharged from the hospital four months after operation.

All the successful cases of resuscitation with intracardiac injections of epinephrin reported in the literature occurred in heart failure following anesthesia, asphyxia, or severe physical or electrical shock, when there was no distinct contraindication to the restoration of the cardiac action, to wit, the presence of a prolonged illness or disease. Only in this type of case would such measures have any permanent effects.

Emergency measures used to restore cardiac activity act either through direct action on the cardiac muscle, as in cardiac massage through the abdomen, or through the action of a drug on the myocardium or on the neuromuscular junctions. Epinephrin injected directly into the heart combines the advantages of the two, the puncture mechanically stimulating the heart muscle, and the drug acting on the neuromuscular junctions.

129 East Sixty-Ninth Street.

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## THE CAPILLARIES OF THE EXTREMITIES IN ACROCYANOSIS

BLOOD PRESSURE AND MORPHOLOGY \*

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The pathologic physiology underlying the condition known as acrocyanosis is not thoroughly understood. In recent years considerable attention has been directed to the part that disorders of the capillaries and venules may play in causing this symptom.

In 1918, Grace Briscoe<sup>1</sup> published observations on the venous and capillary pressures of soldiers, at the Hampstead Military Heart Hospital, who were suffering from "irritable heart." It is well known that such patients often exhibit acrocyanosis to a striking degree. Her method of determining the capillary pressure is similar to that of von Basch. By this method a capsule is affixed to the skin, and air is forced into it until the skin becomes blanched and a further rise of pressure produces no more whitening. The manometric reading at this point is taken as the capillary blood pressure. Using this technic, Briscoe found the capillary blood pressure distinctly elevated in these patients when the hands were blue. When the hands were normal in appearance, the capillary pressure approximated that of the normal controls. Her figures are: Capillary pressure in millimeters of mercury for normal controls, 17.3; for patients when the hands were normal, 19.0, and when the hands were blue, 27.1. The venous pressure in all three groups was about the same.

From these observations, Briscoe concluded that there must be a constriction of the venules sufficient to cause a high capillary pressure without alteration of

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\* From the Medical Division of the Montefiore Hospital for Chronic Diseases.

1. Briscoe, Grace: Observations on Venous and Capillary Pressures with Special Reference to the Raynaud Phenomena, *Heart* 7:35, 1918-1920.

the venous pressure. She further considered the possibility of a simple dilatation of the capillaries, but believed it hardly probable.

In 1920, Danzer and Hooker<sup>2</sup> discussed the wide errors inherent in the method of von Basch, as well as in the other procedures that have been employed in the measurement of the capillary pressure, and described a microcapillary tonometer, by means of which the capillary blood pressure may be estimated with considerable exactitude and with the avoidance of the errors of the older methods. I have discussed the possible inaccuracies of their method elsewhere.<sup>3</sup> While engaged in a general study of the capillary blood pressure by means of Danzer and Hooker's instrument, I have had the opportunity to examine twelve patients who exhibited acrocyanosis from the mildest to the more severe degrees. The technic of the original authors was carefully followed, except that the finger of the patient was not scrubbed, for fear of introducing a complicating factor. The hand was held at the level of the heart during the examination. The results of ten examinations are recorded in the accompanying table.

It is evident that in every case the capillary blood pressure is low. The normal capillary pressure, as determined by this method, varies from 20 to 30 mm. of mercury. Another striking feature is the lack of variability of the capillary pressure. In patients with normal or high capillary pressure, the readings made on different capillaries usually show a variation of about 20 mm. of mercury. In this series the difference between high and low readings never exceeds 10 mm., and in most instances is much smaller.

A further study of some of the individual cases is instructive. The capillary blood pressure varied with the appearance of the hands. Thus, in Case 1, twenty-one readings taken on different capillaries, Aug. 18 and 25 and Sept. 13, 1921, when the hands were normal in appearance, ranged between 13.5 and 26 mm. of mercury. September 8 and October 5, the hands were very cold, pale and cyanotic. The capillary pressure

2. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, *Am. J. Physiol.* **52**: 136 (May) 1920.

3. Boas, E. P., and Frant, Samuel: The Capillary Blood Pressure in Arterial Hypertension, *Arch. Int. Med.* **30**: 40 (July) 1922.

in ten readings registered 2 or 3 mm. of mercury, and in one capillary only was a reading of 17 mm. obtained. The cold hand was then immersed in very hot water and became bright red in color. The capillary pressure, determined immediately, was from 19 to 20 mm. As the hands slowly cooled and again became pale and

#### RESULTS OF EXAMINATION IN TEN CASES OF ACROCYANOSIS

No.	Sex*	Range of Capillary Pressure, Mm. Hg.		No. of Readings	Appearance of Capillaries	Blood Pressure		Appearance of Hands
						Systolic	Diastolic	
1	♂	2 to 3		5	Long; large subcapillary plexus; slow streaming	115	60	Cold, pale, cyanotic
2	♂	7 to 13		13	Very thick, especially at venous end; many bizarre and convoluted with anastomoses; many rows; slow streaming	220	130	Cold, cyanotic, moist
3	♂	5 to 15	24 in two capillaries	14	Thick and convoluted; many large, slow streaming	105	70	Dusky red; slow return of color after momentary pressure
4	♂	3 to 5		20	Numerous, thick and blue, especially the venous loop; many tortuous and bizarre; slow streaming; much stasis	110	80	Cold, moderate cyanosis
5	♀	12 to 15		3	Thick and convoluted	...	...	Cold, moist, red
6	♂	13 to 21		8	Long, somewhat looped; several rows	110	75	Cold, moist, red
7	♂	10 to 13		10	Numerous, not thick; few tortuous; some anastomoses; slow streaming	120	70	Warm; slight cyanosis
8	♂	5 to 13		10	Long, large, thick, especially at venous end; somewhat tortuous; many rows; slow streaming	105	70	Warm, dry; slight cyanosis
9	♂	6 to 10		19	Long, large, thick, especially at venous end; somewhat tortuous; many rows; slow streaming	110	80	Cold, dusky red, moist
10	♀	3 to 7		8	Numerous; many rows; many convoluted and bizarre	125	90	Cold, pale; not cyanotic

\* In this column, ♂ denotes male, and ♀ female.

blue, the readings dropped first to 13 and then to 8.5 mm. It was striking, too, to observe the change in the blood flow in the capillaries. When the hands were cold and blue, the streaming was very sluggish and irregular; but after the hot water bath it became very rapid, and the capillaries became full. Similar observa-

tions were made in Cases 8 and 10. In Case 8, after the hand was warmed, the pressure rose from a range of from 5 to 13 mm. of mercury to a range of from 20 to 27. In Case 10, the pressure before warming was from 3 to 7 mm., and after warming from 7 to 13 mm. In Case 2, thirteen readings, when the hand was cyanotic, ranged between 7 and 13 mm. During the examination the hand became warm, the capillary flow became accelerated and the pressure rose to between 17 and 23 mm.

It is evident from these observations that when the hands are cold and cyanotic, the capillary blood pressure is low and the flow sluggish. This cannot be due to a constriction of the venules, but must depend on a constriction of the arterioles or a marked dilatation of the capillaries. It is significant, too, that the capillaries become fuller when the hands are warm. If the venules were constricted, the capillaries would be engorged during the period of cyanosis.

A number of observations on the capillary blood flow and on the appearance of the capillaries in acrocyanosis have been published. Weiss<sup>4</sup> noted that in patients of an asthenic build, who often exhibit acrocyanosis, the capillaries are more tortuous than normal, particularly in the venous portion, and that the blood stream is slow and may even at times be completely arrested. In the vasoneuroses he saw contractions of the arterial limb of the capillaries in ischemia, and a dilatation of the venous limb when the hands became blue. The appearance of the capillaries, as well as the speed of the blood stream, may vary from moment to moment. Warming the hand accelerates the blood flow in the capillaries.

Mertz<sup>5</sup> found long and tortuous capillaries in children with vasomotor instability. Parrisius<sup>6</sup> observed a movement, which he likened to peristalsis, in the venous arm of the capillaries in a patient with local asphyxia of the feet. This caused an interruption in the continuity of the blood column. He also noted changes in the form of the capillaries in the vasoneuroses. In a case of Raynaud's disease, Weiss saw very wide capillary loops, which exhibited variations in

4. Weiss, E., and Holland, M.: Zur Morphologie und Topographie der Hautkapillaren, *Ztschr. f. exper. Path. u. Therap.* **22**: 108, 1921.

5. Mertz, A.: Kapillarbeobachtungen an Säuglingen, *Deutsch. med. Wehnschr.* **46**: 480, 1920.

6. Parrisius, W.: Zur Frage der Contractilität der menschlichen Hautkapillaren, *Arch. f. d. ges. Physiol. (Pflüger's)* **191**: 217, 1921.



caliber. In a similar case, Pribram and Henius<sup>7</sup> observed a capillary spasm associated with ischemia. Halpert<sup>8</sup> described in detail the capillary changes in a patient with a typical Raynaud's syndrome. She found increased tortuosity of the capillaries, as well as groups of capillaries from three to five times larger than normal. The blood flow was slow. During an attack the giant capillaries became fuller, especially in their venous portion and exhibited changes in contour, such as pro-

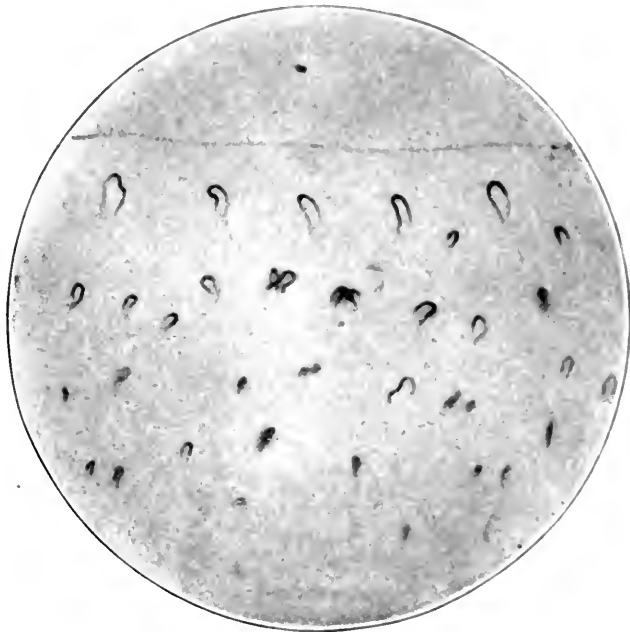


Fig. 1.—Normal appearance of capillaries.

jections and strictures. The blood appeared to be pushed through the vessel by a peristaltic-like wave. In a severe attack the blood became completely stagnant and blue. These observations correspond strikingly to the explanation originally offered by Raynaud.<sup>9</sup>

7. Pribram and Henius: Bemerkungen zum Kapillarbild bei Raynaudscher Krankheit, Berlin klin. Wchnschr. **57**: 67, 1920.

8. Halpert, A.: Ueber Mikrokapillar beobachtungen bei einem Fall von Raynaudscher Krankheit, Ztschr. f. ges. exper. Med. **11**: 125, 1920.

9. Raynaud, M.: On Local Asphyxia and Symmetrical Gangrene of the Extremities, translated by T. Barlow, London, Selected Monographs New Sydenham Society, 1888, p. 144.

I myself have not observed evidences of contractility of the capillaries in patients with vasomotor disturbances of the hands, but I have not had the opportunity of studying a case with a typical Raynaud's syndrome. However, changes in the form of the capillaries are very striking, as is apparent from the table and from the accompanying illustrations. It is difficult to describe the normal appearance of the capillaries at the base of the finger nail, because of their great variability in

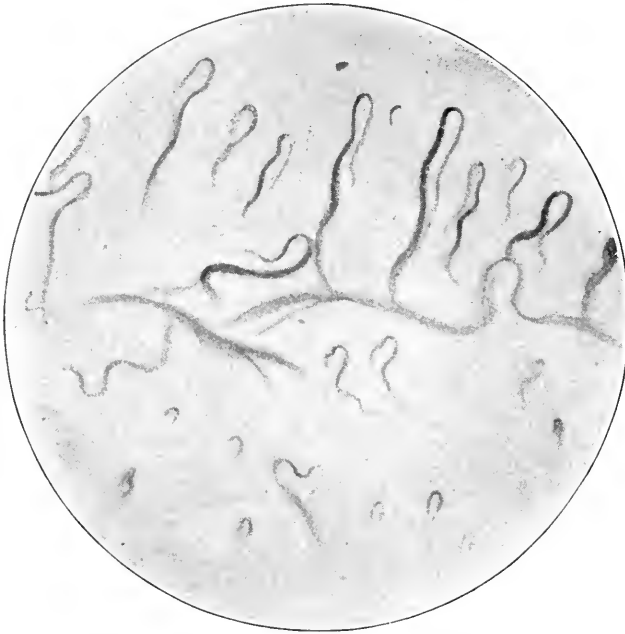


Fig. 2.—Capillaries of normal person with slight vasomotor disturbances of the hands.

structure. Figure 1 represents perhaps the usual picture in healthy persons. Here are seen one or two rows of simple loops near the cuticle, and below them many rows of shorter, more comma-shaped vessels. In patients with chronic vasomotor disturbances of the extremities, the capillaries are usually longer and thicker than normal, particularly in their venous portion, and not infrequently exhibit many convolutions and quite a bizarre arrangement. The rate of the blood

flow varies in different vessels, and usually is slow. The streaming may be completely arrested in groups of capillaries.

Some experiments of Lapinsky<sup>10</sup> suggest a possible cause for this alteration in structure. He studied the capillary circulation in the web of a frog's foot after the corresponding sciatic nerve had been severed. For a short period after the nerve had been cut, the blood flow was slow and the vessels empty. In a few days

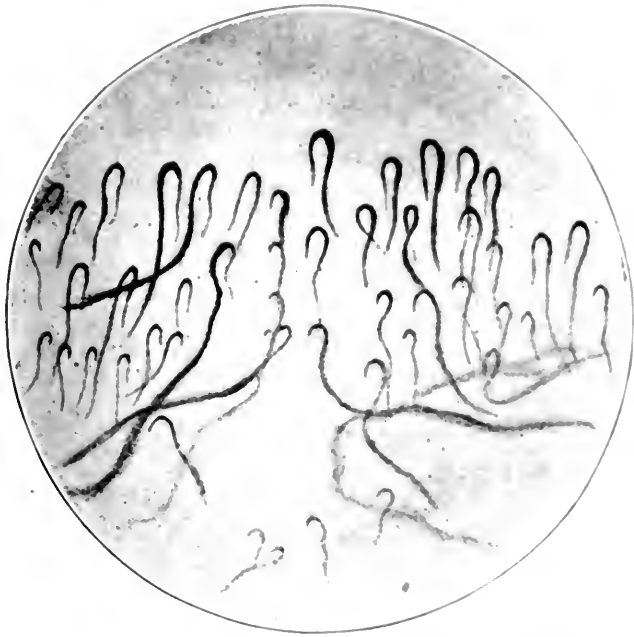


Fig. 3.—Appearance of capillaries in case of acrocyanosis

the capillaries became dilated, and the blood stream became rapid. Later the capillaries became wide and tortuous, and the blood flow again became slow. Lapinsky attributed the change in the form of the capillaries to a loss of elasticity and contractility, which resulted in a widening and a lengthening of the vessel. The convolutions are thus dependent on an increase in

10. Lapinsky, M.: Studien über die locale Blutcirculation im Bereiche gelähmter Nerven, Arch. f. Anat. u. Physiol., Physiol. Abth., 1899, suppl. 477.

length of the capillary, just as the tortuosity of one of the peripheral arteries is dependent on an increase in length. It seems rational to suppose that the morphologic and functional changes in the capillaries of patients with vasomotor disorders are due to a disturbed innervation, which affects them in a similar manner.

#### CONCLUSIONS

In patients with vasomotor disturbances of the extremities, the capillary blood pressure in the fingers is low and the capillary flow is retarded during the period of ischemia or cyanosis. With the return of a normal color of the hands, the capillary pressure, as well as the blood flow, rises and approaches the normal. In most of these patients the capillaries of the fingers are longer and wider than in healthy persons, and often exhibit many convolutions and a bizarre architecture.

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# THE PREVENTION OF SIMPLE GOITER IN MAN \*

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Simple or endemic goiter is one of the most benign and insidious diseases of man and animals. The sum total of its ravages throughout all ages and in all lands is still unrealized by the public generally, notwithstanding the numerous reports of commissions appointed for its study. Those who live on the sea coasts fortunately have had no need to be concerned; and those who lived in goiter districts—before the days of extensive travel—grew accustomed to look on goiter as natural and normal. Indeed, in many districts of the world, it is still looked on as a mark of beauty.

Simple goiter includes all those thyroid enlargements in man and animals formerly grouped as endemic, epidemic, sporadic and physiologic. It must be sharply distinguished from exophthalmic goiter, with which it has no necessary association or etiologic relationship. Exophthalmic goiter, so far as is yet definitely known, occurs spontaneously only in man, while simple goiter occurs in all animals having the ductless thyroid. Exophthalmic goiter is not notably associated with districts, while with simple goiter this is most characteristic. Exophthalmic goiter occurs more frequently in the highly developed and civilized races, while in simple goiter race is not a factor. Simple goiter may develop sporadically in any place (even at sea, as reported on one of Captain Cook's voyages), but it is preeminently

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\* Read before the Section on Pharmacology and Therapeutics at the Seventy-Second Annual Session of the American Medical Association, Boston, June, 1921.

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associated with certain regions or districts. The distribution of these districts of endemic goiter throughout the world was fully described by Hirsch, in 1860. The actual incidence of goiter within a given district is still quite unknown. With the information at present available, however, one can distinguish between mildly and severely goitrous districts. As compared with certain other districts, for example, the Alps and the Himalaya regions, our most important districts, namely, the Great Lakes Basin and the Cascade Mountain regions of Oregon, Washington and British Columbia, would be classified as mildly goitrous. The mildness or severity of a district may be determined by the incidence of myxedema or cretinism—a fact known to Morel and expressed in his famous dictum, “Goiter is the first halting place on the road to cretinism” (*Le goître est la première étape sur le chemin qui conduit au cretinisme*).

#### ETIOLOGY

The ultimate cause of simple goiter is totally unknown, notwithstanding a relatively large amount of study. The immediate cause is a lack of iodine. The enlargement, therefore, is a symptom and may result from any factor which increases the iodine needs of the organism, as in certain types of infection, or which interferes with the normal utilization of iodine; or it may result from actual experimental deprivation of iodine. The conception that it is due to a contagium vivum in the sense that this term is ordinarily used may be abandoned. Water has been associated as an etiologic factor by all peoples as far back as history goes. The American Indians (Barton) and the natives of Central Africa (Livingston) seem to have been as strongly convinced of the relation of water to the disease as was Hippocrates. If water is a factor, it would seem that it is the absence rather than the presence of some substance, which is to be considered, since goiter is associated with the purest of waters, chemically and bacteriologically as, for example, in Portland, Ore., and in Seattle and Tacoma, Wash., where there has been a rapid increase in goiter since these cities began to take their water supplies from the Cascade Mountains. After consideration of all the various substances, agents and theories that have been put forward as having a rôle

in the etiology of goiter, we at present must fall back on the view that thyroid hyperplasia (goiter) is a compensatory reaction arising in the course of a metabolic disturbance and immediately depending on a relative or an absolute deficiency of iodine.

#### PATHOLOGIC ANATOMY

Anatomically, a wide range of changes may be present, depending on the species of animal and on the stage (duration) of the disease. It always begins with a decrease in the colloid material and a hypertrophy of the epithelial cells, at first cuboidal, later columnar, with infoldings and plications. In man and fowls, the stage most commonly observed is characterized by an abundance of colloid material—the so-called cystic or colloid goiter of the older writers—while in dogs, sheep, cattle, pigs, fish, etc., the accumulation of colloid is seen only in the late regressive or quiescent stages. In man, the adenomatous form (*struma nodosa*) is very common, but it is exceedingly rare in all the lower animals. These adenomas, in all probability, arise from fetal cell rests. The stimulus which initiates the growth of the cell rests (adenomas) and that which initiates the growth of the more differentiated thyroid tissue are probably identical. These growths have many of the attributes of tumor, in that their growth may not be arrested by iodine administration or by the natural physiologic compensation.

#### EXPERIMENTAL PHYSIOLOGY

No accomplishment in preventive medicine has a firmer physiologic and chemical foundation than that underlying goiter prevention, and, as the work of prevention is based on certain of these facts, the more important may be reviewed:

1. The active principle of the thyroid is a very stable organic compound of iodine, first recognized by Baumann, in 1895, and recently (1916) isolated in crystalline form, by Kendall.

2. The developmental stage of all goiters is characterized by an increased blood flow, an increase in the size and number of epithelial cells, a decrease in the stainable colloid, and a marked absolute decrease in the iodine store. The decrease in the iodine store precedes the cellular hypertrophy and hyperplasia.

3. Similar changes (compensatory hyperplasia) invariably occur in the remaining portion of the gland, when a sufficient portion of the entire gland is removed. The amount of gland it is necessary to remove in order to cause compensatory hyperplasia varies somewhat with the species of animal, definitely, with the age, diet, and the presence or absence of iodine.

4. The administration of exceedingly small amounts of any salt of iodine in any manner completely protects the remaining thyroid against compensatory hyperplasia, even after the removal of three fourths of the normal gland in cats, dogs, rabbits, rats and fowls. Halsted and Hunnicutt reported a series of partial removals in dogs in which they failed to obtain compensatory hyperplasia, while Loeb has recently reported a series of partial removals in guinea-pigs in which iodine failed to prevent the compensatory hyperplasia, although desiccated thyroid still protected. He concluded that regeneration was physiologically different from spontaneous hyperplasia or simple goiter. The explanation for Halsted's results was probably that the animals were in contact with a source of iodine, while the most probable explanation for Loeb's results is that he removed too much thyroid, since, as shown by Marine and Lenhart, in 1909, iodine will not protect even in dogs if more than three fourths of the gland is removed, while desiccated thyroid will protect the animal against thyroid regeneration even after the removal of as much as nine tenths.

5. If most of the thyroid gland is removed before or in the early stages of pregnancy, and rigid precautions are taken to exclude iodine, the young at birth will have enlarged thyroids, as first shown by Halsted in dogs; while, if iodine is available, the young at birth will have normal thyroids.

6. A milligram of iodine, given at weekly intervals, has been found sufficient to prevent thyroid hyperplasia in pups.

7. Thyroid tissue has an extraordinary affinity for iodine, as has been demonstrated in *in vitro* perfusions of surviving thyroids, and also by injecting intravenously small amounts of some soluble salt of iodine into the intact animal.



8. If the iodine store in the thyroid is maintained above 0.1 per cent., no hyperplastic changes, and therefore no goiter, can develop.

The foregoing experimental data seem to us sufficiently complete to demonstrate the underlying principles of goiter prevention, and the ease with which they may be applied. The first instance in which these facts were utilized in the prevention of goiter on a large scale occurred in 1909 and 1910. Working with endemic goiter in brook trout, Marine and Lenhart were able to demonstrate that iodine added to the water in a concentration not exceeding 1:1,000,000 arrested or prevented the development of thyroid hyperplasia (goiter). Since then, the method has been successfully applied on a large scale by several observers in the prevention of goiter in cattle, sheep, pigs and poultry.

To our knowledge, the prevention of human goiter was not attempted on any large or practical scale until 1917, when we began work with the school population of the city of Akron, although in Cleveland it had been strongly urged and had been used by some physicians for several years. Briefly, the method as applied to man consisted in the administration of 2 gm. of sodium iodide in 0.2 gm. doses, distributed over a period of two weeks, and repeated each autumn and spring. This amount of iodine is excessive, and far beyond the needs of the individual or of the ability of the thyroid to utilize and store it. One gram distributed over a longer period would be better. The form or mode of administration of iodine is of little consequence. The important thing is that iodine for thyroid effects should be given in exceedingly small amounts, and it is believed that most of the untoward effects recorded are due to the excessive doses employed, or, more concretely, to the abuse of iodine.

The results of our two and one-half years' observations on schoolgirls in Akron are as follows: Of 2,190 pupils taking 2 gm. of sodium iodide twice yearly, only five have developed enlargement of the thyroid; while of 2,305 pupils not taking the prophylactic, 495 have developed thyroid enlargement. Of 1,182 pupils with thyroid enlargement at the first examination who took the prophylactic, 773 thyroids have decreased in size; while of 1,048 pupils with thyroid

enlargement at the first examination who did not take the prophylactic, 145 thyroids have decreased in size. These figures demonstrate in a striking manner both the preventive and the curative effects. Klinger has recently (1921) reported even more striking curative results in the schoolchildren of the Zürich district. He worked with school populations in which the incidence of goiter varied from 82 to 95 per cent., while our maximum incidence in Akron was 56 per cent. With such a high natural incidence of goiter, his observations necessarily deal more with the curative effects. Thus of 760 children, 90 per cent. were goitrous at the first examination. After fifteen months' treatment with from 10 to 15 mg. of iodine weekly, only 28.3 per cent. were goitrous, of a total of 643 children reexamined.

The foregoing results were obtained in adolescents. There are two other periods in life when simple goiter frequently develops, namely, (1) in fetal life and (2) during pregnancy. While the thyroid enlargements developing around the age of puberty are more common, they are not more important than those developing during pregnancy and fetal life. The higher birth mortality of infants with congenital goiter is well known. The thyroid enlargement of both mother and fetus may be prevented by giving 2 gm. of sodium iodide, or its equivalent in iodine in any other form, during the first half of pregnancy.

#### UNTOWARD EFFECTS

The dangers of giving iodine, in the amounts indicated, to children and adolescents are negligible. Exophthalmic goiter and iodism are the two important conditions to be looked for. No case of exophthalmic goiter developed in the series reported by Klinger or by us, although in both instances such cases were carefully looked for. Much has been written of iodine-exophthalmic goiters, but a study of the case reports reveals the fact that they resulted from the use of excessive (according to physiologic standards) amounts of iodine, or of desiccated thyroid. In adults, the possibility of aggravating a mild exophthalmic goiter or even the production of the syndrome in susceptible individuals must be considered. Again, the risk is slight. Iodine should not be given in any frank case of exophthalmic goiter

unless the patient can be daily observed, and then it should be administered only in milligram doses. Iodism was observed in eleven cases among the schoolchildren of Akron during the two and one-half years of observation. Most of these cases were very mild, and the girls did not stop the treatment. Klinger did not observe a single instance in sixteen months' observation on more than 1,000 children, although iodism was carefully looked for.

#### SUMMARY

Simple or endemic goiter in man may be prevented as cheaply and as simply as in the lower animals, by the administration of 3 to 5 mg. of iodine twice weekly, over a period of a month, and repeated twice yearly. Klinger in Switzerland has reported as striking, and nearly as extensive, results as those obtained by us in Akron. In young individuals, with goiter of recent development, the curative effects of exceedingly small amounts of iodine are as marked as one sees in the goiter of animals.

There are no dangers worthy of consideration associated with the administration of the quantities of iodine used by Klinger or by us. Simple or endemic goiter most commonly develops during (1) fetal life, (2) around the age of puberty, and (3) during pregnancy, and we believe that any plan which provides for its control during these three periods of life will practically eliminate endemic goiter. Goiter in the mother and fetus can be prevented as simply as that of adolescence, but, practically, it would seem that it is a responsibility of individual physicians, supplemented by public education. The prevention of goiter of childhood and adolescence should be a public health measure, best administered through the schools in order to combine the important additional factor of education. Beginning with the period of puberty, goiter occurs approximately six times as frequently in females as in males. The question, therefore, whether general prophylaxis should include both males and females would depend to some extent on whether the particular district was mildly or severely goitrous; hence the need for accurate surveys. The age of beginning and stopping the use of iodine would depend to some extent on race and climate. In the United States, probably the maximum

of prevention coupled with the minimum of effort would be obtained by giving iodine between the ages of 11 and 17 years.

The prevention of goiter means vastly more than eliminating cervical deformities. It means, in addition, the prevention of those forms of physical and mental degeneration, such as cretinism, mutism and idiocy, which are dependent on thyroid insufficiency. Further, it would prevent the development of thyroid adenomas, which are an integral and essential part of endemic goiter in man, and due to the same stimulus. These multiple, circumscribed benign growths have many of the attributes of tumor, one of which is that their growth once initiated is frequently not controlled by iodine, as are all simple hyperplasias. The terminal metamorphoses are far more serious than those of simple hyperplasia, since, in addition to hemorrhage, necroses, cyst formation, etc., probably 90 per cent. of the malignant tumors of the thyroid arise from these adenomas.

If the prevention of goiter is good preventive medicine, it is better preventive surgery. With so simple, so rational and so cheap a means of prevention at our command, this human scourge, which has taken its toll in misery, suffering and death throughout all ages, can and should be controlled, if not eliminated.

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## AN ADAPTATION OF THE FOLIN AND HU BLOOD SUGAR METHOD APPLICABLE TO SMALL AMOUNTS OF BLOOD\*

A COMPARISON OF THE BLOOD SUGAR CONTENT OF VENOUS AND CAPILLARY BLOOD

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IT is very desirable and in fact often necessary to estimate the blood sugar by some procedure requiring only the small amounts of blood that may be obtained from pricking the finger. Various micro methods of this kind have been used, the Bang,<sup>1</sup> adaptations of the picric acid method of Lewis and Benedict<sup>2</sup> and Dehn and Hartman,<sup>3</sup> and the MacLean,<sup>4</sup> being among those more commonly employed. The Bang procedure while long and most exacting, is so apt to give erroneous results that analyses must be done in triplicate. The picric acid method of Epstein<sup>5</sup> has often been found to yield results considerably higher than those obtained by other procedures and we have had similar experiences with it. Like all colorimetric methods in which the color measured is the resultant of two or more colors, in this case sodium picrate and sodium picramate, serious errors are often introduced as shown by Falk and Noyes.<sup>6</sup> The work of the Harriman Research Laboratory investigators has raised a serious objection on both theoretical and practical grounds, to the use of any picric acid reduction method, where another procedure is available. The MacLean method seems to have yielded excellent results though it is quite long and great care is said to be necessary.

When the systematic methods of blood analyses of Folin and Hu<sup>7</sup> were published, they were tried out in this laboratory, and after thorough testing, found to be very satisfactory, and adopted as our standard procedures. With a view to keeping our methods limited to trustworthy ones, and as few as possible, we endeavored to adopt the blood sugar method of Folin and Hu for an amount of blood that could be obtained by pricking the finger. This we have succeeded in doing in a very satisfactory way, using 0.4 c.c. of blood. The adaptation is comparatively simple and rapid and is free from the objections that have just been pointed out. It has been in use here and at other laboratories for the past two years. The procedure is as follows:

Ordinary one c.c. serologic pipettes, graduated to the tip, in 0.01 c.c. are cut off at about the 0.6 c.c. mark and calibrated to the 0.4 c.c. mark. The pipette is connected with a rubber tube, on the end of which a small glass mouthpiece is placed. Blood is obtained, usually from the fourth, occasionally from the middle finger of the left hand by pricking with a Hagedorn needle.

\*From the Laboratories, Montefiore Hospital, New York.  
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Gentle pressure is applied if necessary, not too near the wound, until a large drop of blood has collected. This is carefully drawn up the pipette, in the beginning mainly by capillarity, but after about 0.2 c.c. of blood has been obtained, very gentle suction must be applied to the glass mouthpiece. The surface of the skin is kept quite dry with sterile sponges to keep the blood in a deep round drop; if the skin is not dry the blood will spread.

After 0.4 c.c. of blood has been obtained, it is immediately discharged into a 5 c.c. tube graduated in 0.1 c.c. containing about one c.c. of distilled water. The corpuscles settle to the bottom of the tube and a clot will form unless the tube is gently rotated. Frothing should be avoided. The pipette is then quickly washed with water several times, the washings added to the tube and the total volume brought to 3.2 c.c. Four tenths of a c.c. of ten per cent sodium tungstate and an equal volume of 0.7N sulphuric acid are added successively, the tube is closed with a cork or rubber stopper, shaken vigorously and allowed to stand ten or fifteen minutes. Then centrifuge in the same tubes for ten or fifteen minutes at a high speed. Filter the supernatant liquid through a very small filter ( $4\frac{1}{4}$  cm.) into a 15 c.c. or 30 c.c. beaker.

Two c.c. of the filtrate are pipetted into a Folin sugar tube and Folin and Hu's procedure followed exactly as in the macro method. That is, 2 c.c. of standard sugar solutions, equivalent to 100 and 200 mgs.\* of glucose per 100 c.c. respectively, are pipetted with Folin-Ostwald pipettes into similar sugar tubes. To both the unknown and the standards, 2 c.c. of the faintly alkaline copper tartrate solution are added and all heated simultaneously in a boiling water-bath for exactly six minutes. The tubes are then quickly plunged into cold water and kept there for two minutes, after which two c.c. of the molybdate phosphate solution are added to each. The tubes are shaken vigorously, allowed to stand about five minutes, made up to 25 c.c. and matched. Not more than four tubes should be heated at once unless more than one person can be at hand so that the molybdate phosphate solution can be added nearly simultaneously to all the tubes. The color remains practically unchanged for more than one hour.†

A comparison of results obtained by the micro and macro methods is presented in Table I.

\*Containing 0.2 and 0.4 mg. of glucose respectively.

† For convenience, the preparation of reagents as described by Folin and Hu is given:

*Ten per cent Sodium Tungstate.*—Purchased from the Vanadium Corporation of America, Primos, Delaware Co., Pa. Labelled Primos Brand and C. P.

*Alkaline Copper Tartrate Solution.*—Dissolve 40 gms. of pure anhydrous sodium carbonate in about 400 c.c. of water and transfer to a liter flask. Add 7.5 gms. of tartaric acid and when the latter has dissolved add 45 gms. of crystallized copper sulphate. Mix and dilute to one liter. If the reagents used are impure a sediment of cuprous oxide may separate in the course of one or two weeks. Should this occur, remove the clear supernatant fluid with a siphon or filter through a good quality filter paper. To test for the absence of cuprous copper, in the solution, transfer 2 c.c. to a test tube and add 2 c.c. of the molybdate phosphate solution; the deep blue color of the copper solution should almost completely vanish.

*Standard Sugar Solutions.*—Three standard sugar solutions should be on hand: (1) a one per cent pure glucose solution, which is kept as a stock solution, preserved with a thin layer of toluene or xylene; (2) a solution containing 1mg. of glucose per 10 c.c. (5 c.c. of stock solution diluted to 500 c.c.); (3) a solution containing 2 mg. of sugar per 10 c.c. (5 c.c. of stock solution diluted to 250 c.c.). The diluted solutions are also preserved with a little toluene or xylene. The diluted solutions will not keep for much more than a month in warm weather, but the stock solution should keep indefinitely.

*Molybdate Phosphate Solution.*—Transfer to a liter beaker 35 gms. of molybdic acid and 5 gms. of sodium tungstate. Add 200 c.c. of 10 per cent sodium hydroxide and 200 c.c. of water. Boil vigorously for 20 or 40 minutes so as to remove nearly the whole of the ammonia present in the molybdic acid. Cool, dilute to about 350 c.c. and add 125 c.c. of concentrated (85 per cent) phosphoric acid. Dilute to 500 c.c.

TABLE I

	COMPARISON OF MACRO AND MICRO METHODS		REMARKS
	MACRO	MICRO	
Mrs. P.	174	174	Diabetic
A. B.	105	105	
A. I.	150	155	After lunch
Mrs. H.	320	323	Diabetic coma
Dog 1	100	96	
Dog 2	132	130	During absorption
Dog 2	241	239	1 1/2 hrs. after glucose administration
Sheep 1	75	77	

In Table II the results of analyses of blood, drawn successively from the median cephalic vein and finger tip are given. After the blood was drawn from the arm, it was immediately taken to the laboratory and precipitated according to the method of Folin and Hu. As soon as blood had been drawn from the vein, specimens were obtained from the finger tip and analyzed by the method just described.

TABLE II

	COMPARISON OF BLOOD SUGAR CONTENT OF VENOUS AND CAPILLARY BLOOD	
	VENOUS BLOOD MG. PER 100 C.C.	CAPILLARY BLOOD MG. PER 100 C.C.
N. B.	100	107
Mrs. P.	129	139
M.	98	108
H. S.	104	101
O. L.	92	96
? W.	120	123
? K.	101	103
B. J.	246	247
E. J.	386	390
? R.	94	99
D. C.	135	142
D. C.	117	121
L. R.	111	106
? R.	119	110
L.	92	96
Dr. A.	100	103
W.	128	128
W. D.	103	102
M. S.	106	102
S. S.	94	95
D. C.	114	116
	105	95
S. W.	90	95
H. P.	139	136
M. G.	132	134
F. I.	106	107

As might be expected on theoretical grounds, the capillary blood usually contained very slightly more reducing substances than venous blood. However, these variations may have been due to a little glycolysis of the venous blood. Occasionally on account of the distance from the wards as much as ten or fifteen minutes elapsed between the time the blood was drawn and the proteins precipitated, while in the case of the micro determinations, the precipitations were made at once.

Glucose solutions added to blood were in every instance recovered quantitatively by the above described micro method.

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## CLINICAL REPORT OF A CASE OF GRAVES' DISEASE WITH RAPID IMPROVEMENT FOLLOWING THE ORAL ADMINISTRATION OF FRESH OX SUPRARENAL GLAND

S. SHAPIRO and DAVID MARINE

From the Laboratories of Montefiore Hospital, New York.

The following clinical report of a case of exophthalmic goiter presents several unusual features in addition to the classical manifestations of profound asthenia, emaciation, tachycardia, thyroid hyperplasia, tremor and exophthalmos. The more important of these were:

- (1) Periods of pyrexia for which no assignable cause could be found;
- (2) Very low systolic blood pressure;
- (3) Purpura with prolonged bleeding time, decreased platelet count, swollen and bleeding gums and a history of profuse menstrual hemorrhage; and,
- (4) A rapid gain in weight and muscular strength, rise in blood pressure and decrease in bleeding time associated with administration of fresh ox suprarenal gland, but without any noteworthy changes in the pulse rate, exophthalmos or thyroid gland.

*Case History:* R. B., the patient, is a female, age 30 years, single, and a stenographer by occupation.

*Family History:* This is unimportant.

*Past History:* Aside from measles and diphtheria, the patient has never had any serious illness.

*Habits:* The appetite is always good. The bowels were regular until about two years ago. Since then she has been irregularly constipated.

*Weight:* Her average weight before the present illness was about 125 pounds.

*Menstruation:* Began at the age of thirteen and has been regular up to August, 1919.

*Present Illness:* During June of 1919 the patient first noticed the occurrence of irregular large and small black and blue spots on her thighs. She consulted her physician, who treated her without improvement. Soon the spots spread so that they were present on the abdomen and chest. These purpuric spots continued to develop for more than a month when, early in August of 1919, the patient developed a sudden profuse menstruation which lasted for sixteen days. She became so exsanguinated that a blood transfusion was performed. She also became very nervous, complained of palpitation of the heart, persistent dryness of the mouth, and increased muscular weakness. Nocturia two or three times each night developed about this time. A second uterine hemorrhage occurred at the time of the next menstrual period and is said to have ceased following the administration of thromboplastin. At this time abnormal prominence of the eyes was noted, her nervousness became more marked, the palpitation of the heart and dryness of the mouth persisted. She was losing weight steadily in spite of a good appetite. Physical weakness became profound. Purpuric spots covered her chest, abdomen, upper and lower extremities.

Her case was now recognized as one of exophthalmic goiter and she was advised to go to the mountains for a rest. She remained in the mountains two months and returned home in December of 1919 feeling better. Her menstrual periods during October and November of 1919 were within normal limits. In December of 1919 she had another profuse menstrual hemorrhage lasting fifteen days, which is said to have been controlled by the administration of thromboplastin. She then went to the country and remained until March, 1920. During these three months the menstrual periods appear to have been normal. However, her exophthalmos had increased so that her ability to read was impaired. There was further loss of weight and muscular strength. Her pulse rate averaged about 150 at that time. There has been amenorrhea since May of 1920.

Early in June of 1920 she went to a western sanitarium, where she remained for four months. Examination of the blood at that time revealed: Red cells, 3,300,000; white corpuscles, 12,700; hemoglobin, 73 per cent. The blood pressure was 150-60. The Wassermann reaction was negative; non-protein blood nitrogen was 25.3; and blood sugar, 100. The urine showed no albumin, sugar, casts or blood cells. The basal metabolic rate in June was + 68. Soon after her arrival at the sanitarium she had, according to her physician, a hemorrhage into the medulla, causing paralysis of the muscles innervated by the 7th, 9th and 12th cranial nerves on the left side. In the course of a few weeks the paralysis cleared up entirely. The purpuric condition,

however, persisted, so that she had considerable oozing from the gums and purpuric spots over the body. X-ray and radium applications to the thyroid were followed by violent reactions. Ligation of the left superior thyroid artery was performed September 1, 1920, and of the right superior thyroid artery on September 25, 1920. Following this, she improved sufficiently to return to New York about October 15th, at which time her metabolic rate was  $-49$ .

She entered Montefiore Hospital October 20, 1920, complaining of nervousness, palpitation of the heart, profound muscular weakness and marked loss in body weight.

*Physical Examination: General:* The patient is a female adult, white, markedly emaciated and so weak that she is scarcely able to stand long enough to have her weight taken. The weight is 70 pounds. She perspires freely. The *Head* is normal in size and shape. The *Hair* is very thin and dry. The *Eyes* show marked bilateral exophthalmos. The pupils are equal and react sluggishly to light and accommodation. Von Graefe's and Stellwag's signs are present. Iritis is present in the left eye. The left fundus shows a petechial hemorrhage near the center of the disc. The right fundus is normal. *Ears:* The hearing is good. No topi, no discharge, no mastoid tenderness are found. *Nose:* There are scab-like crusts of old and recent hemorrhages on the mucous membrane just within the external nares. *Mouth:* The teeth are fairly well kept, the gums are swollen and spongy; there is oozing of blood from the gum margins. The tongue protrudes in the mid-line, is markedly tremulous and dry. Facial muscles show no abnormalities. *Neck:* A transverse scar is seen just above the level of the cricoid cartilage. The thyroid gland is symmetrically enlarged; a thrill is felt and bruit heard over each lobe. Carotid pulsations are forcible and visible. The cervical lymph glands are not enlarged. The *Chest* is of the flat type. The mammary glands are atrophic. The ribs are very prominent. Purpuric spots are seen over the chest. Marked suprasternal pulsations are visible. The lungs are clear and resonant throughout. *Heart:* The cardiac rate is 128. The beat is regular. The apex is in the fifth interspace in the mid-clavicular line; the apex beat is diffuse but forcible. The area of cardiac dulness is not increased. A soft, blowing, systolic murmur is heard over the apex; it is not transmitted. The *Abdomen* is scaphoid. Purpuric spots are seen chiefly over the lower portion. The abdominal wall is very thin. The liver, spleen and kidneys are not palpable. No masses are felt; no tenderness is detected. *Extremities:* No abnormalities are palpable in the long bones. There are a few purpuric spots on the arms and legs. The outstretched fingers show fine tremor. *Reflexes:* The knee jerk and ankle jerk are active. The abdominal reflexes are present. *Temperature:* The temperature of the patient has been ranging between  $100^{\circ}$  and  $102^{\circ}$  since admission.

*Subsequent Notes:* October 26. The patient's temperature still varies between  $100^{\circ}$  and  $102^{\circ}$ . She perspires readily, although kept

quiet in bed. Bleeding along gum margins is seen; calcium lactate, 1 gram t. i. d., is prescribed. Blood examination on this date showed: red cells, 3,800,000; white cells, 9,000; neutrophils 64%, lymphocytes 30%, mononuclears and transitionals 4%, eosinophils 2%; bleeding time eight minutes. The blood pressure was 95-60, the weight, 72½ pounds. Urine had a specific gravity of 1010, was acid, showed a very faint trace of albumin, with no sugar and no casts.

October 27. Glucose tolerance test using 50 grams of glucose gave no glycosuria in three hours.

October 31. The tolerance test was repeated, using 100 grams of glucose. No glycosuria appeared in three hours.

November 1. Started desiccated suprarenal gland, 0.3 grams t. i. d. The bleeding time was eight minutes. The weight was 70½ pounds.

November 4. The patient still complains of persistent dryness of the mouth. The temperature is normal for the first time since admission. The blood pressure is 100-60.

November 9. The patient is on a full diet. She is out of doors most of the day, but still unable to walk. Her weight is 73 pounds.

November 13. The blood pressure is 105-65.

November 16. The weight is 74 pounds.

November 18. Dryness of mouth and sweating persist. Coarse tremor of fingers is apparent.

November 22. Fresh ox suprarenal gland, 10 grams, t. i. d., is substituted for the desiccated suprarenal. The weight is 75½ pounds. The blood pressure is 115-75.

November 23. The patient had nausea and vomiting associated with cramp-like pains in the abdomen, probably due to the excessive administration of fresh suprarenal gland. This is discontinued.

November 27. Desiccated whole suprarenal gland, 0.3 gram, t. i. d., is started. The blood pressure is 110-70.

November 29. Desiccated suprarenal gland is discontinued and the administration of fresh whole ox suprarenal, 5 grams daily, begun. The weight is 75 pounds.

December 2. Temperature has remained normal since November 28. Between November 6 and November 28 the temperature has fluctuated between normal and 102°. The bleeding time is four minutes. The patient no longer complains of dryness of the mouth nor of sweating—symptoms that have been present since admission. She is now able to walk from bed to porch. New growth of scalp and axillary hair is visible. Urine examination shows: specific gravity, 1012; acid, very faint trace of albumin; no sugar; no casts.

December 6. The weight is 77 pounds. The blood pressure is 110-70.

December 12. Blood examination shows: red cells, 4,000,000; white cells, 7,500; neutrophils, 62%; lymphocytes, 30%; mononuclears and transitionals, 6%; eosinophils, 2%.

December 13. The weight is 83 pounds. The blood pressure is 115-70.

December 21. The weight is 87¼ pounds. The blood pressure is 115-70.

December 27. The exophthalmos seems slightly increased. The outstretched fingers show marked lessening of tremor. The patient is able to walk about the ward without dyspnea. The purpuric spots have disappeared. The weight is 94 pounds. The blood pressure is 115-70.

January 1. Temperature arose to 100.2° today. The abdomen is distended with gas. Nausea is complained of. Colonic irrigation and light catharsis are administered.

January 3. The temperature is normal. The abdomen is soft.

January 4. The weight is 99¼ pounds. The blood pressure is 120-70.

January 9. Fresh suprarenal gland is discontinued (for a control period). The patient still receives calcium lactate.

January 11. The weight is 101¼ pounds.

January 15. The blood pressure is 125-70.

January 18. The weight is 108 pounds. The temperature has remained normal since January 3. The patient feels quite comfortable. Palpitation and tremor are improved. The blood pressure is 120-70. The bleeding time is four minutes. Urine examination shows: specific gravity, 1010; very faint trace of albumin; no sugar; no casts.

January 25. The weight is 113 pounds.

January 31. The weight is 117¼ pounds. The bleeding time is five minutes.

February 1. Purpuric spots reappear over chest and thighs. Feeding 5 grams of fresh ox suprarenal cortex daily is begun. Blood examination shows: red cells, 4,150,000; white cells, 4,500; platelets, 40,000; neutrophils, 64%; lymphocytes, 26%; mononuclears and transitionals, 10%. The bleeding time is 4½ minutes.

February 5. The patient is menstruating for the first time in nine months.

February 6. The temperature is elevated to 101.4°. The patient complains of headache and diarrhea.

February 7. The temperature is 100.8°.

February 8. The temperature is 101.8°. Diarrhea is still present. The blood pressure is 125-70.

February 9. The temperature is 102.4°.

February 10. The temperature is 102.8°. A severe chill was experienced during the night. The blood pressure is 125-70. The abdomen is distended. Tenderness is elicited over both ovaries. The bleeding time is four minutes.

February 11. The temperature is 102.8°. The stools are normal. The purpuric spots have disappeared.

February 13. The temperature is 99.4°. Desiccated ox suprarenal cortex, 0.3 grams, t. i. d., is substituted for the fresh suprarenal gland.

February 14. The weight is  $112\frac{1}{2}$  pounds. The temperature is normal.

February 21. Purpuric spots have returned. Desiccated whole suprarenal gland is substituted for the desiccated cortex. The weight is  $115\frac{3}{4}$  pounds.

February 24. The blood pressure is 125-80.

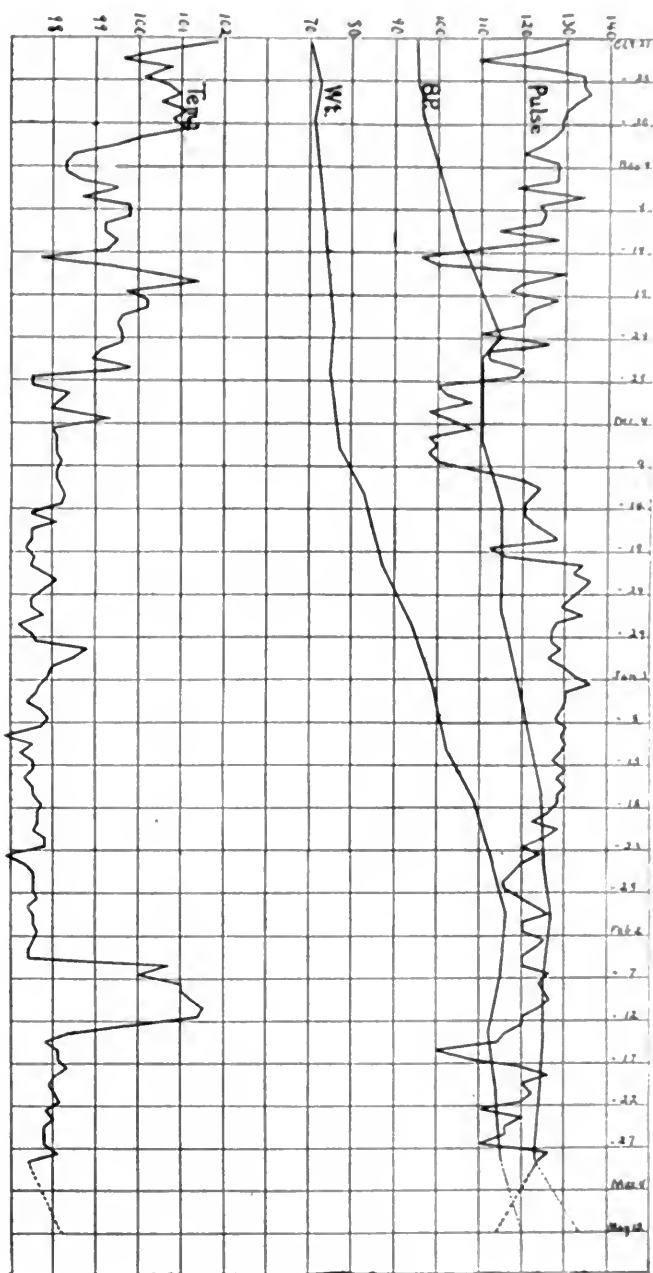
March 1. Purpuric spots are still present on the chest. The patient feels quite comfortable and is able to take considerable exercise without fatigue. She leaves the hospital today.

May 12. The patient returns for observation after having spent approximately  $2\frac{1}{2}$  months in the country. The temperature is  $98.2^{\circ}$ ; the pulse, 112; blood pressure, 120-76; weight, 133 pounds. There is no tremor of the outstretched fingers. Muscular strength is excellent. Exophthalmos is possibly slightly less. There is no abnormal sweating. She sleeps well. Her appetite is good. A thick coat of scalp hair has grown. The skin is normal. The neck measures 34 cm. in circumference; the thyroid gland is vascular. The menstrual function has been regular. Purpura is absent. Subjectively the patient is quite comfortable and able to take considerable exercise daily without fatigue. Since leaving hospital the patient has taken one gram desiccated whole suprarenal gland daily.

#### DISCUSSION

Fever in uncomplicated exophthalmic goiter is rare, although patients suffering from this disease frequently complain of hot flushes and of feeling warm. If fever is present, it usually manifests itself as a very slight and fairly constant elevation of the temperature above normal. The febrile reaction in this case suggested a focal infection, but we were unable to find such a focus, and moreover there was no leukocytosis, nor did the pulse vary with the temperature.

Extensive studies on blood coagulation in exophthalmic goiter have been made in Kocher's clinic. These have uniformly shown a prolongation of the coagulation time in frank cases. Purpura is a rare complication. In our case exacerbations and remissions were observed which coincided with the withholding and administration of suprarenal gland. The bleeding time likewise increased and decreased with the appearance and disappearance respectively of the purpura. The patient showed a marked and rapid gain in weight, which began with the administration of desiccated suprarenal gland, and became more rapid after the fresh gland was substituted. Others, including Solis-Cohn and Cray, have observed rapid increases in the weight following the



administration of suprarenal gland. Oppenheim and Hoppe have reported similar rapid gains following the use of desiccated ovary and corpus luteum. Quite recently, Obregia has reported a series of twenty-one cases of exophthalmic goiter, including classical types as well as the so-called "formes frustes," in which he obtained a marked and rapid amelioration of the symptoms, excepting exophthalmos and tachycardia, by the administration of from 10-50 drops of a glycerol extract of whole fresh pig suprarenal gland by mouth. This author also claims that adrenalin alone seemed to have some beneficial effect, but negligible as compared with the glycerol extract of whole fresh gland. He was aware of the voluminous literature now available dealing with the untoward effects of adrenalin in exophthalmic goiter, and of the alleged hypersecretion of epinephrin in this disease.

Unfortunately, we were unable to make metabolic rate determinations during the period under observation, although in June a rate of + 68, and in September, a rate of + 49 were obtained in another institution. The right and left superior thyroid arteries were ligated September 1st and 25th, respectively. While increase in weight and general improvement frequently occur within two or three weeks after ligation, it is quite unusual to see such marked gains in weight unaccompanied by pulse and thyroid changes beginning after an interval of two months without improvement.

The systolic blood pressure remained relatively constant at 95 mm. for the first ten days after admission, and during the next  $2\frac{1}{2}$  months rose gradually to 125 mm. This likewise was coincident with the gain in weight and the administration of suprarenal gland. We do not believe there is any direct relationship between the administration of the suprarenal gland and the rise in blood pressure, and are inclined to believe that the improved vascular tone is more readily explained as a part of the general improvement. Other striking evidences of improvement were the return of the menstrual function and the new growth of scalp and axillary hair, the disappearance of the asthenia, the lessening of the tremor, the disappearance of abnormal sweating and dryness of the mouth, although the thyroid gland, as regards size, consistency, bruit and expansile pulsation, remained unchanged, as did also the pulse rate and exophthalmos throughout her stay of over four months in the hospital.

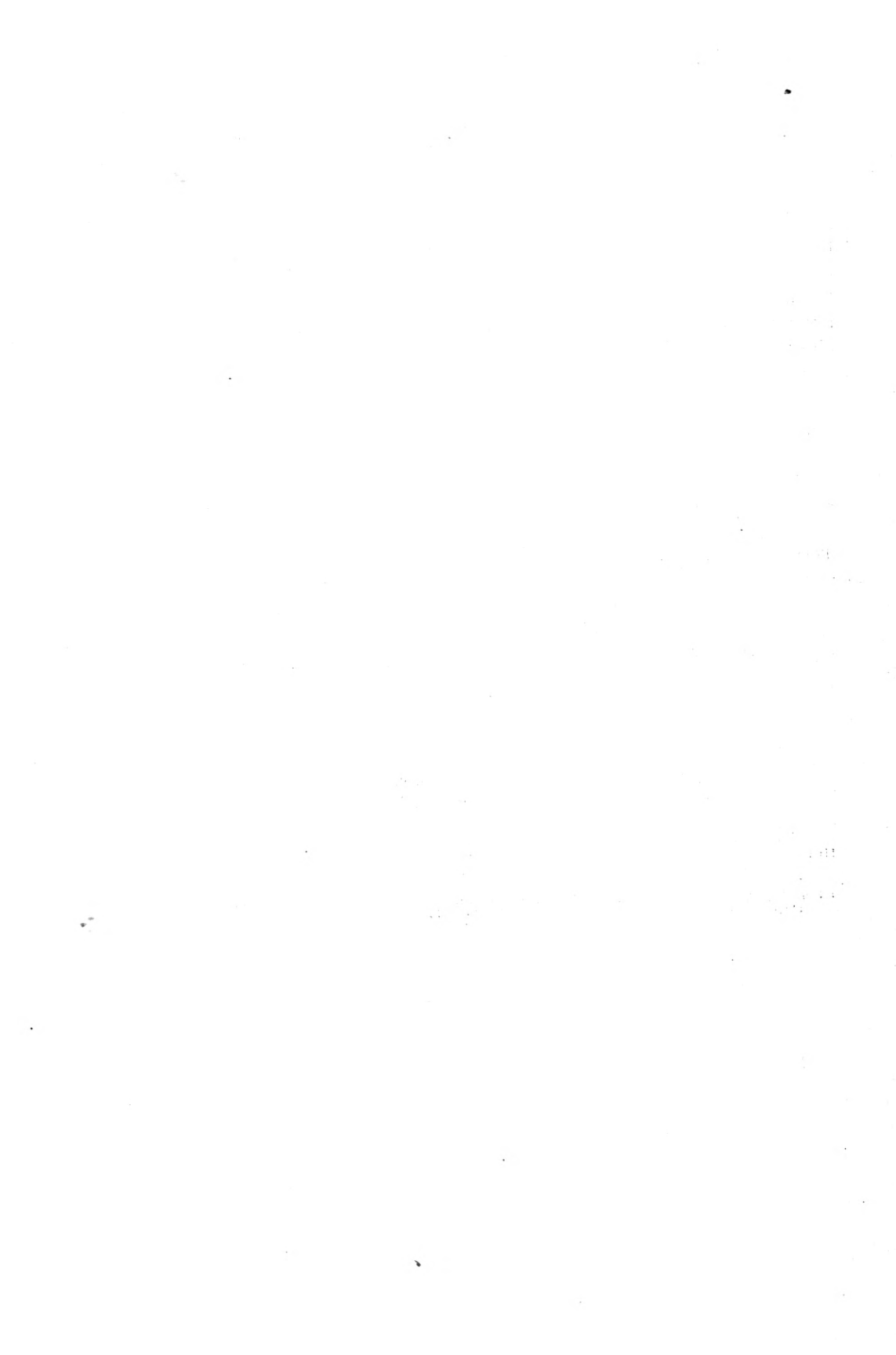


## SUMMARY

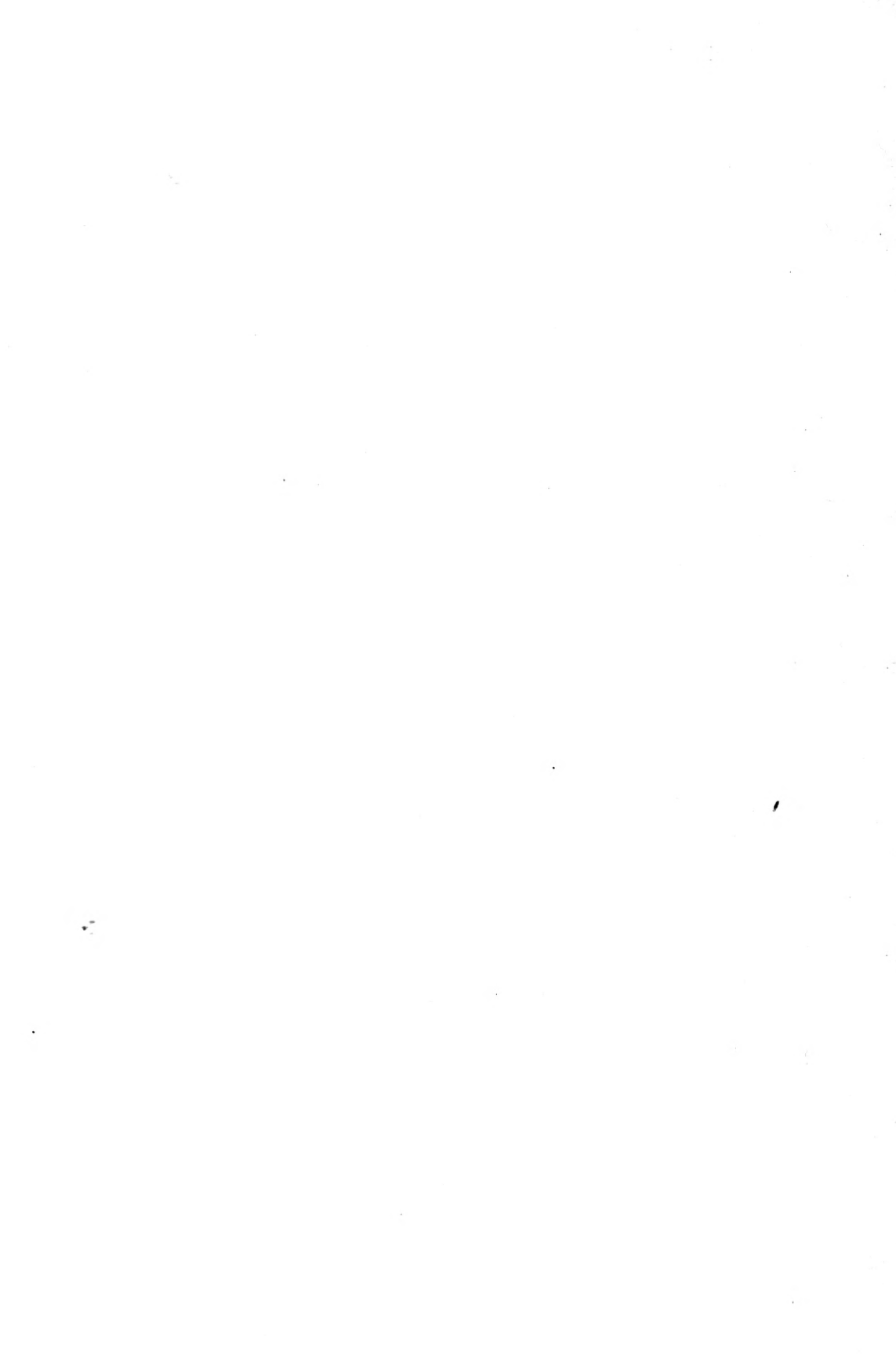
Very rapid and striking improvement in the general nutrition of a case of exophthalmic goiter has been observed following the use of suprarenal gland. This improvement occurred during the administration of fresh ox suprarenal cortex, rather than during the administration of desiccated suprarenal gland. The observation contains an additional suggestion from the clinical viewpoint of a possible relative functional insufficiency of the suprarenal cortex as one of the underlying factors in exophthalmic goiter. Our experience suggests that fresh suprarenal cortex may be administered in five gram doses daily by mouth without untoward effects. Larger doses, especially of whole fresh suprarenal gland, caused nausea and vomiting, probably from direct irritation of the gastric mucosa by epinephrin. These doses are equivalent to much larger amounts of desiccated suprarenal gland than had been administered by the authors of the reports above referred to. Evidence, both experimental and clinical, is now rapidly accumulating that the suprarenal gland, and particularly its cortical portion, plays an essential and fundamental role in the etiology of exophthalmic goiter.

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## INFLUENCE OF GLANDS WITH INTERNAL SECRETION ON THE RESPIRATORY EXCHANGE

### II. EFFECT OF SUPRARENAL INSUFFICIENCY (BY REMOVAL OR BY FREEZING) IN RABBITS<sup>1</sup>

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The fact that animals which survive double suprarenalectomy for a week or more, frequently lose weight rapidly was pointed out by the earliest observers (1), (2), (3), (4). This loss of weight is largely due to the rapid disappearance of fat. Likewise, Porges (5), Schwartz (6) and many others have shown that suprarenalectomy causes a rapid disappearance of glycogen from the liver and a progressive fall in the blood sugar in dogs and rats. Notwithstanding these striking manifestations of suprarenalectomy their possible relation to alterations in the rate of metabolism seems to have attracted very little attention.

Golyakowski (7) in 1899 published a preliminary report on his observations on twelve dogs in which most of the blood supply to the suprarenals was blocked by mass ligation (the exact nature of this operation is not given). He reported that three died within 3 days, one lived 28 days and eight survived longer than 6 weeks. In those animals which survived over 6 weeks, he noted a rise up to 30 per cent in heat production and CO<sub>2</sub> output within the first 10 days, followed by a drop nearly to normal, then a second rise as high as 50 per cent between the 2nd and 4th weeks falling to or even below normal about the 6th or 7th week. Heat production and heat loss were parallel, from which he concluded the heat regulating mechanism was intact. While emphasizing the increase in heat and CO<sub>2</sub> production, he also states there was little or no increase in O<sub>2</sub> consumption above the normal. He realized the discrepancy between the CO<sub>2</sub> and O<sub>2</sub> values, but he

<sup>1</sup> Presented in abstract—Society for Experimental Pathology, Chicago, December 28, 1920.

explained the low  $O_2$  intake by assuming that the extra necessary  $O_2$  was derived from the tissues. On account of this statement together with the absence of any experimental data or descriptions of methods used one cannot attach the importance to his conclusions to which they would otherwise be entitled. We have been unable to find any other references to work on the effect of removal of the suprarenal glands on the respiratory exchange except that reported by Aub (8) and his co-workers. They reported briefly the effects of suprarenalectomy on the respiratory exchange in three cats and found "there was a slight rise in the metabolic rate for some hours, and 48 hours after operation a sharp fall to about 25 per cent below normal. This remained until the animals were sacrificed 5 days after operation." At the same meeting we reported strikingly different observations on the effects of suprarenalectomy on the respiratory exchange in rabbits. It is, therefore, the purpose of this paper to report in some detail the types of modification observed in the respiratory exchange.

Our experience with suprarenalectomized cats has been strikingly similar to that of Aub, except that the deterioration of the animals as measured by the metabolic rate and duration of life was even more rapid. Cats, dogs and guinea pigs usually survive the operation of double suprarenalectomy, whether performed at one or two sittings, only a few days. This fact limits the study of the metabolic changes to the immediate or acute effects of suprarenal insufficiency. White rats withstand double suprarenalectomy too well. The wide variation in duration of life following double suprarenalectomy in rabbits makes it possible easily to obtain metabolic studies on a series of animals surviving the operation from a few days on to indefinite survival. The varying lengths of time which rabbits survive extirpation of the suprarenals is believed to depend upon the presence of varying amounts of accessory cortical tissue, lying for the most part in the neighborhood of the suprarenal glands or along the path of migration of the sex glands. Paradoxical as it may seem the presence of accessory cortical tissue makes it possible to obtain more graded series of incomplete suprarenalectomies than can be obtained by attempting to leave intact varying amounts of the main glands. This is due to the impossibility of preserving unimpaired the blood supply of the unremoved portion. The importance of keeping this in mind becomes even greater if we realize how small a fragment of functionally active suprarenal cortex suffices to maintain the animal in apparently normal health. It was for these reasons that the rabbit was selected as being the most suitable animal for this study.

*Methods.* The respiratory exchange was determined with the Haldane apparatus, modified as described in a previous paper (9). Rabbits were kept under comparatively uniform conditions. Their diet consisted of alfalfa hay, oats and carrots. They were last fed 15 or 16 hours before the respiratory exchange was determined. The gaseous exchange was determined for a period of 2 hours in each instance. Forty-two rabbits have been used. Control metabolic rates were obtained for a period of several weeks, sometimes before removal of the right suprarenal and sometimes after its removal. No significant change in the metabolic rate or departure from the normal behavior of the animal has been noted following the removal of one suprarenal except in one instance (rabbit 216). In a small group (seventeen) the attempt was made to destroy the function of the cortex of one or both glands by freezing and at the same time to leave the medulla intact. This was done by isolating the gland with as little injury to its blood vessels and nerves as possible and freezing for 30 to 45 seconds with a spray of ethyl chloride. In several instances we succeeded in severely injuring most of the cortex except that portion immediately adjacent or within the medulla, while at the same time preserving most of the medulla with its blood supply intact, as determined later histologically. The method of separating medulla from cortex by freezing, while highly efficient and simple, could not be utilized in effecting a complete separation in rabbits because of the anatomical relationships of cortex and medulla. Likewise, it is not readily applicable to the right suprarenal in this animal because of the relation of the gland to the vena cava. Marked suprarenal insufficiency has been obtained in a number of instances by this method without destroying the medulla as determined by the physiological behavior of the animal and histological examination.

*Presentation of data.* The following eight protocols have been selected from the 42 experiments of this series as types of the alterations observed in the respiratory exchange. These types may be divided more or less arbitrarily and for convenience of presentation into 3 groups, depending on the completeness of removal and the time of survival, namely:

I. Those that live indefinitely after removal or injury of the suprarenals with no appreciable alteration in the respiratory exchange.

II. Those that show an increase in the respiratory exchange followed by a fall, to, or below normal, whether dying within 2 or 3 weeks or living on indefinitely.

III. Those that show a fall of the metabolic rate beginning within 48 hours after the removal or injury of the glands and continuing to death.

In addition to these groups representing suprarenal injury or removal, it has seemed advisable to add for the sake of comparison one protocol showing the effect of desiccated thyroid feeding in a "normal" rabbit.

GROUP I. *Protocol I.* Rabbit 232; female.

November 26, 1920. Under ether removed right suprarenal completely

December 5, 1920. Wound healed, stitches removed, weight 2810 grams.

December 22, 1920. Began metabolic studies

January 8-11, 1921. Gave total of 0.4 gram potassium iodid by mouth

January 24, 1921. Gave birth to young—destroyed

February 25, 1921. Injected 0.5 gram cholesterol (from gallstones) intraperitoneally

March 22, 1921. Under ether removed left suprarenal completely

March 31, 1921. Wound healed

April 19, 1921. Died this morning, necropsy, body still warm, pregnant near term, 6 embryos; ovaries very large, pale yellow, five distinct corpora lutea; thymus present; thyroids vascular; parathyroids vascular; liver large, pale grayish yellow brown, nutmeg appearance, fatty. Whitish subcapsular deposits probably cholesterol; kidneys enlarged, cortex swollen, grayish and possibly fatty; heart moderate hypertrophy; right and left suprarenal glands absent; no accessories found on careful search; spleen normal in size; solitary gastric ulcer about 1 cm. from pylorus; death probably from acute suprarenal insufficiency developing late in, and in relation to pregnancy with renal and hepatic lesions resembling those of toxæmia of pregnancy.

*Protocol II.* Rabbit 255, female

March 2, 1921. Began metabolic studies

March 22, 1921. Under ether the right and left suprarenals were exposed through usual incisions for removal and frozen with ethyl chloride spray; the blood vessels were not divided

April 1, 1921. Wounds healed and stitches removed

April 15, 1921. Healthy, strong, killed, immediate necropsy. All viscera appear normal, except suprarenals; right suprarenal easily isolated, upper portion firm, yellow brown, while portion on inferior cava shows soft, vascular, pale yellow, normal-looking cortical mass approximately  $3 \times 3$  mm.; left suprarenal readily enucleated, upper portion dry, firm, yellow brown with grayish tint, lower portion of gland adjacent renal vein is soft vascular and measures approximately  $2 \times 2$  mm.; no accessory suprarenals found; both ovaries enlarged, pale yellow and contain several large Graafian follicles; thymus atrophic; thyroid normal in size and color.

GROUP II: *Protocol III.* Rabbit 217, male; adult

September 17, 1920. Started metabolic studies

October 21, 1920. Under ether removed right suprarenal completely

October 28, 1920. Superficial wound infection

November 16, 1920. Under ether removed left suprarenal completely, enlarged

November 18, 1920. Soft stools, dull, eats fairly well

November 28, 1920. Not eating well, getting weaker, wounds healed



TABLE 1

*Rabbit 232*

DATE	WEIGHT OF RABBIT.	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALOR- IES 2 HOURS*	CALORIES PER KG. PER HOUR	REMARKS	
1920										
December 22.	2916	4.295	5.230	0.52	0.46	88	14.83	2.54	November 26. Right suprarenalectomy (complete)	
1921										
January 13...	3153	4.675	4.965	0.52	0.40	77	15.64	2.48		
February 9...	2745	4.085	5.095	0.52	0.47	91	14.07	2.56		
February 21...	2764	4.275	4.855	0.54	0.45	83	14.40	2.60		
February 26...	2712	3.770	4.025	0.49	0.38	78	12.55	2.31		
March 1.....	2812	3.730	4.780	0.46	0.43	93	12.98	2.31		
March 4.....	2843	4.505	5.380	0.55	0.48	87	15.39	2.71		
March 8.....	2839	4.120	4.555	0.51	0.41	80	13.92	2.45		
March 16....	2903	4.515	5.350	0.54	0.47	86	15.44	2.66		
March 24....	2800	4.315	4.920	0.54	0.45	83	14.60	2.61	March 22. Left supra- renalectomy (complete)	
March 26....	2780	4.375	5.265	0.55	0.48	88	14.93	2.68		
March 30....	2776	3.970	4.400	0.50	0.40	80	13.44	2.42		
April 4.....	2670	3.645	3.945	0.48	0.38	78	12.30	2.30		
April 15....	2817	4.040	4.200	0.50	0.38	75	13.51	2.40		

\* Calculated from CO<sub>2</sub> for all tables.

TABLE 2

*Rabbit 255*

DATE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALOR- IES 2 HOURS	CALORIES PER KG. PER HOUR	REMARKS
<i>1921</i>									
March 2	2998	3.895	4.465	0.45	0.38	83	13.25	2.21	March 22. Right and left suprarenals frozen
March 10	3013	3.555	4.070	0.41	0.34	83	12.08	2.00	
March 21	3026	3.875	4.225	0.45	0.36	79	13.04	2.15	
March 24	2917	3.585	3.925	0.43	0.34	79	12.11	2.08	
March 26	2953	3.880	4.535	0.46	0.39	85	13.21	2.24	
March 30	2961	3.745	3.980	0.44	0.34	77	12.54	2.12	
April 4	2965	3.660	3.945	0.43	0.34	78	12.30	2.07	
April 15	2902	3.695	4.035	0.45	0.35	79	12.45	2.14	

December 27, 1920. Slow deterioration to death on this date, immediate necropsy; thyroids not enlarged; parathyroids normal; patchy consolidation of left lung; right lung free; heart not enlarged; both kidneys are small and "spotted." The spots are due to congested depressions in cortex. On section grayish streaks and focal areas are present both in cortex and pyramidal portion; right and left suprarenals absent; no accessories found; thymus large and cellular; lymph glands of mesentery and retroperitoneum enlarged; no visible abdominal fat.

TABLE 3  
*Rabbit 217*

DATE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALOR- IES 2 HOURS	CALORIES PER KG. PER HOUR	REMARKS
<i>1920</i>									
September 17.	2424	3.600	3.877	0.52	0.41	78	12.08	2.49	October 21. Right suprarenalectomy complete  November 16. Left suprarenalectomy complete
November 8..	2590	4.180	4.580	0.57	0.45	79	14.13	2.73	
November 18.	2450	4.385	4.990	0.63	0.52	83	14.81	3.02	
November 20.	2482	4.330	4.710	0.61	0.48	79	14.54	2.93	
November 22.	2462	4.410	4.775	0.63	0.49	79	14.74	2.99	
November 24.	2582	4.450	5.010	0.60	0.49	82	15.01	2.91	
December 2..	2478	3.730	4.165	0.53	0.43	81	12.60	2.54	
December 8...	2510	4.000	4.715	0.56	0.48	85	13.73	2.73	
December 15.	2522	4.070	4.965	0.56	0.50	90	13.83	2.74	
December 21..	2466	3.370	3.905	0.48	0.40	85	11.37	2.31	

*Protocol IV. Rabbit 237*

December 7, 1920. Under ether removed right suprarenal completely

December 9, 1920. Began metabolic studies

January 8-11, 1921. Gave total of 0.4 gram potassium iodid

January 25, 1921. Under ether exposed and froze left suprarenal, with ethyl chloride leaving blood vessels intact

January 30, 1921. Fairly active, eats oats, hay and carrot

February 15, 1921. Active, gave birth to one full-term fetus, destroyed

February 18, 1920. Dull, eats very little

March 15, 1921. In good condition, eats moderately of oats, hay and carrot

March 16, 1921. Died about 6 hours after removal from respiratory chamber, necropsy at once; thyroids small, clear, translucent (iodin effect); parathyroids hyperemic; thymus fatty, little lymphoid tissue; lungs clear; heart not dilated; liver normal in size and consistency, congested; spleen congested; pancreas

hyperemic; left suprarenal present as a flaccid, brownish yellow, encapsulated mass,  $10 \times 6 \times 4$  mm., no evidence of any normal cortical tissue; microscopically the tissue is nowhere necrotic; a small oval central area in the lower half of the gland around the suprarenal vein approximately  $3.5 \times 1.5$  mm. is composed of normal-looking medulla, taking a normal chrome stain, extremely vascular. The entire medulla appears to be present; toward the periphery of the medulla mass there are islands of large, granular, normal-staining cortical cells. Beyond this the cortical tissue is shrunken, with numerous cholesterol crystal spaces and cholesterol giant cells; the cortical cells are non-granular, nearly stainless or slightly bluish (with H. and E. stain, the cytoplasm of normal cortex cells takes

TABLE 4  
*Rabbit 237*

DATE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALORIES 2 HOURS	CALORIES PER KG PER HOUR	REMARKS
1920									
December 9.	2267	3.625	4.035	0.56	0.45	81	12.20	2.69	December 7. Right suprarenalectomy complete
December 14.	2315	3.685	4.790	0.56	0.53	95	12.79	2.78	
1921									
January 13.	2462	3.460	4.800	0.49	0.50	101	12.33	2.50	Figures on basis of 100 R. Q.
January 27.	2550	3.290	3.595	0.45	0.35	79	11.08	2.17	January 25. Left suprarenal frozen
February 2.	2447	3.635	4.400	0.52	0.46	88	12.47	2.55	
February 8.	2389	3.900	4.540	0.57	0.48	84	13.33	2.79	
February 11.	2455	4.145	5.135	0.61	0.53	90	14.29	2.91	
February 15.	2285	3.795	4.280	0.58	0.48	82	12.82	2.81	
February 18.	2252	3.570	4.485	0.55	0.51	91	12.38	2.75	
February 23.	2212	3.390	4.590	0.54	0.53	98	11.96	2.70	
February 28.	2262	3.320	4.105	0.51	0.46	90	11.43	2.53	
March 8. . . .	2225	3.355	3.550	0.53	0.41	77	11.18	2.51	
March 16. . . .	2486	3.380	3.635	0.48	0.37	78	11.33	2.28	

eosin); the capillaries are intact and contain blood. This is an excellent example of the preservation of almost if not the entire medulla of the left suprarenal with serious injury of nearly all of the cortex with the preservation of a good blood supply to both parts. Two very small, yellowish white nodules on perirenal fat above and external to kidney; right suprarenal absent; both kidneys show shallow, dark red, pitted areas scattered over cortex; on section there are streaks and rounded areas of greyish lymphoid-like tissue in both the cortical and pyramidal portions; ovaries slightly enlarged, follicles present; abundant fat in all depositories; stomach contains fair amount of food, no ulcers present. Death related to period in metabolism chamber.

*Protocol V.* Rabbit 206; male; adult

April 22, 1920. Weight 2350 grams. Under ether removed right suprarenal completely

April 29, 1920. Wounds healed—weight 2270 grams

June 7, 1920. Began metabolic studies

October 11, 1920. Under ether removed completely left suprarenal, much enlarged, weight 0.461 gram; animal very mangy, coat dull

October 16, 1920. Eats heartily of oats, hay and carrot, soft stools, mange disappearing

October 20, 1920. Mange nearly gone, coat getting glossy, very active, restless, but fatigues easily, wound healed

October 25, 1920. Eats heartily, drinks more water, periods of fatigue and dullness increasing in duration, although restless and active between, losing weight

TABLE 5

*Rabbit 206*

DATE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALOR- IES 2 HOURS	CALORIES PER KG. PER HOUR	REMARKS
<i>1920</i>									
June 7 . . . . .	2390	3.570	3.740	0.52	0.40	76	11.90	2.49	April 22. Right supra- renalectomy complete
June 19 . . . . .	2400	3.610	4.170	0.53	0.44	84	12.26	2.55	
September 11. . . . .	2743	3.365	3.820	0.43	0.35	83	11.33	2.07	October 11. Left supra- renalectomy complete
October 12. . . . .	2306	3.245	3.410	0.49	0.38	76	10.85	2.35	
October 14. . . . .	2480	4.365	5.625	0.62	0.60	93	15.27	3.08	
October 19. . . . .	2405	4.350	4.837	0.63	0.51	80	14.78	3.07	
October 22. . . . .	2275	4.635	4.845	0.71	0.54	76	15.42	3.39	
October 25. . . . .	2280	4.344	4.827	0.67	0.54	81	14.60	3.20	

October 28, 1920. Died this morning, immediate necropsy, weight 2197 grams; thyroids not enlarged; parathyroids hyperemic; thymus present and cellular; lungs congested, no consolidation; right heart dilated; spleen normal; liver dark brown red and much reduced in size; pancreas hyperemic; right and left suprarenals absent, wound healing complete; no accessories found; stomach small, contracted, three small ulcers in pyloric portion; intestines nearly empty, contracted; testes small, flaccid; no visible fat in the usual depositories; mesenteric and regional lymph glands prominent; typical suprarenal death.

*Protocol VI.* Rabbit 251; female; adult

February 15, 1921. Began metabolic studies, coat dull, slight mange and alopecia about eyes

March 14, 1921. Under ether exposed right and left suprarenals, through usual incisions and froze both glands with ethyl chloride; blood vessels left intact.

March 23, 1921. Both wounds completely healed, rapid growth of hair over shaved areas; eats heartily of oats and hay and carrot, is gaining weight rapidly, coat becoming glossy, mange about eyes disappearing

TABLE 6  
*Rabbit 251*

DATE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN °C.	CO <sub>2</sub> PER GRAM PER HOUR IN °C.	R. Q.	TOTAL CALORIES 2 HOURS	CALORIES PER KG. PER HOUR	REMARKS
<i>1921</i>									
February 15	2057	3.250	4.215	0.55	0.52	94	11.35	2.76	
February 24	2410	3.420	4.075	0.57	0.49	87	11.65	2.76	
March 4	2157	2.830	4.040	0.46	0.48	104	10.38	2.41	Figured on basis of 100 R. Q.
March 16	2105	3.540	4.365	0.59	0.53	89	12.27	2.91	March 14 Right and left suprarenals frozen
March 18	2283	4.190	6.050	0.64	0.67	105	15.54	3.40	Figured on basis of 100 R. Q.
March 21	2435	4.300	6.180	0.62	0.65	104	15.88	3.26	Figured on basis of 100 R. Q.
March 23	2406	4.430	5.310	0.64	0.56	87	15.19	3.16	
March 25	2556	4.650	6.425	0.64	0.64	100	16.51	3.23	
March 28	2470	4.405	5.585	0.62	0.58	92	15.29	3.10	
March 31	2525	4.145	5.115	0.57	0.52	90	14.25	2.82	
April 2	2599	4.735	6.385	0.63	0.63	98	16.66	3.21	
April 4	2580	4.220	5.090	0.57	0.50	88	14.43	2.80	
April 7	2613	4.150	5.140	0.56	0.50	90	14.31	2.74	
April 11	2627	3.735	4.745	0.50	0.46	92	12.99	2.47	
April 15	2555	3.790	4.070	0.52	0.41	78	12.69	2.51	
April 19	2511	2.975	3.515	0.41	0.36	86	10.14	2.02	
April 21	2507	3.175	3.620	0.44	0.37	82	10.85	2.16	
April 26	2497	3.160	3.570	0.44	0.36	82	10.70	2.14	
May 3	2613	3.585	4.445	0.48	0.43	90	12.38	2.37	
May 9	2491	3.420	3.885	0.48	0.40	82	11.64	2.34	
May 16	2533	3.405	3.990	0.47	0.40	85	11.62	2.29	
May 19	2507	3.150	3.670	0.44	0.37	85	10.69	2.13	

April 15, 1921. Clean, sleek, active, well-nourished, eats entire ration

May 1, 1921. Appetite during last 2 weeks seems increased

May 15, 1921. Seems in perfect health, consumes food ration rapidly

May 20, 1921. Sacrificed, animal apparently in excellent health, necropsy; thyroids and parathyroids of normal size and appearance; thymus present and cellular; lungs and heart normal; spleen soft, possibly slightly enlarged; liver dark brown red, possibly somewhat reduced in size, flabby and tough; kidneys

small and smooth, uniformly grayish brown in color; right suprarenal involved in slight adhesions, measures  $10 \times 6 \times 3$  mm.; about half of the gland appears normal while the remainder shows the effect of freezing; left suprarenal easily isolated, measures  $11 \times 7 \times 3$  mm., there are large masses of normal looking cortical tissue at each pole, while the middle portion is shrunken yellowish brown from the freezing; no accessories found; ovaries not enlarged; abundant abdominal fat; stomach filled with food, mucosa normal.

GROUP III: *Protocol VII.* Rabbit 257; male; adult

March 14, 1921. Under ether removed right suprarenal completely, enlarged, weight 0.40 grams

March 18, 1921. Began metabolic studies

March 30, 1921. Wound healed completely

TABLE 7

*Rabbit 257*

DATE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALORIES 2 HOURS	CALORIES PER KG. PER HOUR	REMARKS
<i>1921</i>									
March 23 . . .	2250	3.460	4.715	0.54	0.53	99	12.21	2.71	March 14. Right suprarenalectomy complete
March 31 . . .	2290	3.720	4.230	0.57	0.47	83	12.55	2.74	
April 11 . . . .	2315	3.505	4.125	0.53	0.45	86	11.90	2.57	
April 21 . . . .	2214	3.660	4.085	0.58	0.47	81	12.36	2.79	
April 30 . . . .	2105	3.100	3.570	0.51	0.43	84	10.49	2.48	April 28. Left suprarenalectomy complete
May 2 . . . . .	2045	3.160	3.825	0.54	0.48	88	10.84	2.6	
May 5 . . . . .	1965	2.505	2.745	0.45	0.36	80	8.39	2.13	
May 7 . . . . .	1908	2.285	2.470	0.42	0.33	79	7.6	2.00	

April 28, 1921. Under ether removed completely left suprarenal, much enlarged, weight 0.72 gram

April 29, 1921. Active, ate entire ration of oats, hay and carrot

May 1, 1921. Ate very little, looks dull, soft stools

May 7, 1921. Losing weight rapidly, dull, gave 6 grams glucose by mouth

May 8, 1921. Died during night, necropsy; thyroids enlarged and congested; parathyroids congested; thymus present and cellular; lungs and heart normal; liver reduced in size, dark red; spleen normal; pancreas congested; right and left suprarenals completely removed; a 1 mm. grayish, translucent flattened body (accessory cortical mass) on inferior cava just below right renal vein; kidneys appear normal; intestinal tract practically empty; no ulcers in stomach; wounds completely healed; no visible fat anywhere; testes appear normal; typical sub-acute suprarenal death.

*Thyroid Feeding Experiment: Protocol VIII.* Rabbit 250; adult; female  
February 15, 1921. Strong vigorous rabbit. Began metabolic studies

March 4, 1921. Began feeding 0.1 gram very active desiccated sheep thyroid, (containing 0.155 per cent iodine) on alternate days. This thyroid was prepared November 6, 1911, and its pharmacological activity has been tested many times since then, and again this spring on tadpoles, 50 mgm. causing complete metamorphosis in 10 days

March 13, 1921. Looks somewhat dull, fur more erect

March 16, 1921. Gave last of six 0.1 gram doses desiccated thyroid

April 15, 1921. Normal appearance, active

May 15, 1921. Active, healthy, eats all of ration

TABLE 8  
*Rabbit 250*

DATE	WEIGHT 40 RABBIT	O <sub>2</sub> IN GRAMS 2 HOURS	CO <sub>2</sub> IN GRAMS 2 HOURS	O <sub>2</sub> PER GRAM PER HOUR IN CC.	CO <sub>2</sub> PER GRAM PER HOUR IN CC.	R. Q.	TOTAL CALOR- IES 2 HOURS	CALORIES PER KG. PER HOUR	REMARKS
1921									
February 15.	2483	3.940	5.595	0.55	0.57	103	14.37	2.89	Figured on basis of 100 R. Q.
February 23.	2425	3.665	4.195	0.53	0.44	83	12.45	2.57	
March 2. ....	2455	3.715	4.475	0.53	0.46	88	12.69	2.58	
March 5. ....	2413	4.135	4.595	0.60	0.48	81	13.90	2.86	March 4. 0.1 gram thyroid, alternate days
March 7. ....	2419	4.020	4.800	0.58	0.51	87	13.73	2.84	
March 9. ....	2477	4.400	5.165	0.62	0.53	85	15.04	3.04	
March 11. ....	2553	4.200	5.650	0.58	0.56	98	14.74	2.89	
March 13. ....	2490	4.080	5.250	0.57	0.54	93	14.25	2.86	March 14. Last dose thyroid
March 15. ....	2586	4.815	6.200	0.65	0.61	94	16.70	3.23	
March 17. ....	2605	4.030	4.755	0.54	0.46	86	13.72	2.63	
March 19. ....	2665	4.070	4.850	0.53	0.46	87	13.87	2.60	
March 25. ....	2575	3.695	4.665	0.50	0.46	91	12.88	2.50	
April 7. ....	2731	3.630	4.300	0.46	0.40	86	12.41	2.27	

*Group I.* This group includes those animals that survived indefinitely the operation of double removal or injury of the suprarenal glands and whose respiratory exchanges varied less than 10 per cent from their normal average basal metabolism. Fourteen, or 33 per cent, of the rabbits fall in this group. All of these animals with one exception (rabbit 232) that have died or been killed have shown considerable active cortical tissue, either as accessory suprarenals or as unremoved fragments of the main glands or as cortical tissue which had been unin-

jured in the process of freezing. In view of the previous work of other observers and of our previous experience, it is reasonable to suppose that this animal had accessory cortical tissue somewhere to meet its ordinary demands. The failure to find accessory cortical tissue is of little significance since a complete examination would require microscopic examination of serial sections of the entire area within which cortical tissue might occur.

Protocols I and II (rabbits 232 and 255) have been selected as types. In rabbit 232 both suprarenals were removed at two operations, while in rabbit 255 both suprarenals were frozen at a single operation. In rabbit 232 the right suprarenal was removed 26 days before metabolic studies were begun. A series of nine observations extending over the next 3 months was obtained before, and five observations after removal of the second suprarenal. Both glands were completely removed. The respiratory exchange and the body weight remained relatively constant throughout the  $4\frac{1}{2}$  months under observation and death occurred near the end of pregnancy associated with lesions of the kidney and liver closely resembling those of the toxemia of pregnancy. In several instances where pregnancy has supervened in animals surviving double suprarenalectomy in apparent health, death has occurred near the end of pregnancy with the lesions above mentioned.

In rabbit 255, three control observations were obtained over a period of 20 days before freezing and five observations over a period of 24 days after freezing both glands. The respiratory exchange and the body weight remained strikingly constant throughout the period of observation. The animal was apparently in excellent health when killed to terminate the experiment. At necropsy while the greater portion of each suprarenal body was injured, there were masses, approximately  $3 \times 3$  mm. in the right and  $2 \times 2$  mm. in the left, of normal suprarenal gland containing both cortex and medulla.

*Group II.* This group includes those animals that showed, following the double removal or injury of the suprarenal glands, increases in their metabolic rates, followed by a fall to or below the normal whether dying within 2 or 3 weeks or living on indefinitely. This increase in the metabolic rate was observed in 24 animals (of which 7 had one or both glands frozen), or 57 per cent of the series and varied from 10 per cent to 63 per cent above the control. The average maximum increase for the group was 23 per cent.

Protocols III, IV, V, VI (rabbits 206, 217, 237, 251) have been selected as types to show the variations in the degree and duration of the increase



and that these effects may be produced either by removal or injury (freezing) of the suprarenals.

In rabbits 206 and 217 both suprarenals were removed at two operations, while in rabbit 237 the right was removed and the left frozen at two operations and in 251 both were frozen at a single operation. The rise in the metabolic rate usually is manifest on the 2nd or 3rd day while the maximum rise occurred in from 2 days to 3 weeks or more. Sometimes the metabolic rate rose gradually to a peak followed by a gradual fall to or below normal. Not infrequently, however, the rate rose and fell two or three times before finally falling to or below normal.

Rabbit 237 showed a rise of approximately 9 per cent, reaching its maximum on the 17th day after freezing the second suprarenal. Rabbit 217 showed a maximum rise of 12 per cent, reaching its maximum 6 days after removal of the 2nd suprarenal. Rabbit 251 showed a maximum rise of 28 per cent reaching its maximum 4 days after freezing both suprarenals, remained approximately at this level for the next 11 days, then gradually fell to or below normal during the next month. During the period when the heat production was increasing rapidly the respiratory quotients for this rabbit were above 1. The animal was killed to terminate the experiment 67 days after freezing both glands, at which time it appeared normal in all respects.

Rabbit 206 showed a progressive rise reaching its maximum of 42 per cent above its normal on the 11th and 14th days, following removal of the second suprarenal. The animal died on the 17th day without any observations after the 14th day. This rabbit lost weight rapidly although he ate voraciously—an excellent example of rapid tissue as well as food oxidation. The rise in all instances was absolute as indicated by both the total heat production and the  $\text{CO}_2$  output.

Certain clinical phenomena have been observed in the animals of this group which are strikingly different from those of other groups. The operation wounds healed more quickly and the hair has grown more rapidly over the shaved areas than those of group 1. The nutrition of the skin improved as shown in certain instances where coats previously dull, dry and mangy became clean and glossy. In many instances the animals showed increased appetite. Soft stools so commonly observed following suprarenalectomy in rabbits were always most pronounced during the period of rising metabolic rate. Animals with increased metabolic rates were more active, more restless, more easily irritated and sometimes became vicious. They likewise became fatigued very

quickly. Evidence of increased sexual activity was also observed. In general the animals showing the greatest rise lost weight in spite of a food intake often larger than their average normal.

*Group III* includes those animals that survived the operation of double removal or injury of the suprarenals from a few hours to a few days. Only 4 or 9 per cent of the rabbits of the series fall in this group. In the case of cats, dogs and guinea pigs, this group would be much the largest. The metabolic rate shows a fall beginning within 48 hours after suprarenalectomy. In certain experiments a slight rise may precede the fall, in others this is absent. The rapidly fatal outcome and the fall in the respiratory exchange are parallel phenomena and depend, it is believed, upon the completeness of destruction of cortical function. Protocol VII (rabbit 257) showing a fall of 26 per cent in heat production below its normal illustrates the group. The period of survival was somewhat prolonged (9 days) but on this account the progressive fall in the metabolic rate is more definite.

*Thyroid feeding.* Protocol VIII (rabbit 250) is introduced to show the effect on the respiratory exchange of feeding desiccated thyroid to normal rabbits and for comparison with the effects of suprarenalectomy. One-tenth gram of an active preparation was given by mouth every other day for 12 days. An irregular rise in the heat production reaching 20 per cent above the control rate on the 11th day resulted. The desiccated thyroid was discontinued after 6 doses and the rate rapidly returned to the normal average. The rise in the heat production following the thyroid feeding was less than the average obtained following suprarenalectomy.

#### DISCUSSION

It appears established that by removing or crippling (by freezing) the suprarenal mechanism a disturbance in the metabolic rate characterized by an increased heat production may be brought about. This disturbance appears definitely related to the completeness of removal of suprarenal function and the duration of life. If only one gland is removed usually no noteworthy changes follow. Even when both are removed there may be no change in the animal's behavior or in its metabolic rate. In such cases one can almost always demonstrate the presence of accessory masses of suprarenal cortex. In most instances (57 per cent of this series) where both glands were removed or crippled there was a progressive rise in the metabolic rate. Sixty-eight per cent of the rabbits in which both suprarenals were removed and 41

per cent of those in which one or both suprarenals were frozen showed an increased heat production. This rise is highly variable both in degree and in duration—no two rabbits showing the same response, irrespective of age or sex. Rabbits show wide variations in their normal basal metabolism though it is relatively constant for a given rabbit over a long period of time. In our series “normals” have varied between 2.1 and 3.2 calories per kilogram per hour, the mean and average being 2.5 calories. Eighty-five per cent varied within 12 per cent of the average.

The increased metabolic rate following suprarenal injury may continue for 1, 2, 3 or more weeks with or without slight remissions and is succeeded by a gradual fall continuing to death or if the animal survives indefinitely, to or slightly below its control rate.<sup>2</sup> Occasionally rabbits surviving indefinitely show more than one period of increased metabolism before the metabolic rates finally become stable at or below the control level. In animals dying within a week following suprarenal injury a rise may not be detected (if observations are made on alternate days, as was the usual procedure in these experiments) or if present, may be quickly succeeded by a decrease continuing until death.

Infection or febrile reaction of other origin or trauma of operation may be eliminated as a cause for the rise. The trauma of operation was approximately the same throughout this series, whether removal was complete or not. But in those where complete removal of the right suprarenal was impossible because of its location, no change in metabolic rate was observed following removal of the second.

The protocol showing the effect of feeding desiccated thyroid was introduced in order to compare the effects on the metabolic rate produced by thyroid feeding with those produced by suprarenal injury. The rise resulting from thyroid feeding was 20 per cent in this instance, which is much less than has been frequently obtained following suprarenalectomy, although the dose used was large and pharmacologically the preparation was very active as shown by its ability to cause complete metamorphosis of tadpoles within 10 days. The comparatively small rise in heat production caused by thyroid feeding suggests that the rabbit is not highly susceptible or is incapable of reacting to the same extent that other animals do. If either of these suggestions is true, and

<sup>2</sup> Rabbits, though to a lesser extent than cats and dogs, show the effect of training. They are more restless the first two or three times they are placed in the chamber. The higher control rates and the lower metabolic rates after a few weeks or months may be thus partially explained.

if the increased heat production following suprarenalectomy depends upon the thyroid, it is probable that animals more susceptible to thyroid feeding will show greater reactions following injury to the suprarenals than will rabbits.

No conclusions have been arrived at regarding the mechanism of the rise in the metabolic rate following suprarenal injury. We have developed a working hypothesis which is as follows: Supposing the intact thyroid gland to be the major factor in the maintenance of a given metabolic rate and that this function is controlled by some regulatory mechanism; we have argued that possibly this control might be exercised by a restraining influence, a major factor in which was the normal function of the suprarenal glands. If such should be the case, the removal or crippling of this restraining or inhibitory influence would allow the thyroid to increase its activity. The frequency with which thyroid and thymus hypertrophy occur after suprarenalectomy in rabbits is additional evidence of the possibility of increased thyroid activity. One cannot neglect to consider the possibility, indeed the probability, of vastly more extensive disturbances in the functions and interrelationships of other organs than the thyroid. There is other evidence that suggests a more general regulatory or inhibitory function of the suprarenal gland. In suprarenalectomized animals there is increased sexual desire, increased intestinal peristalsis associated with soft stools, and increased mobilization of sugar. Wound healing and the growth of hair over shaved areas may be more rapid than ordinarily. The fur over the whole body often became smooth and more glossy. Such animals are usually more irritable and even become vicious. There is sometimes evidence of increased appetite. We have noticed instances where in association with a rise of the metabolic rate there was an increase in body weight associated with respiratory quotients above 1. All these phenomena might be interpreted as suggesting that the suprarenal glands may normally exercise a regulatory action over many body functions. Renal lesions have been observed in a significant number of rabbits surviving suprarenalectomy from 3 to 5 weeks. They have not been detected in rabbits dying within 10 days. The changes have been briefly described in protocols III and IV. Marshall and Davis (10), working with cats, showed there was a definite increase in the urea and creatinin content of the blood in suprarenalectomized cats, but were unable to detect any renal lesions, though carefully looked for. In rabbits we have also observed distinct increases in the urea and creatinin content of the blood in animals after

the onset of the marked terminal asthenia, although at the height of the increased metabolism these substances usually are within normal limits. The possibility of injury to the renal function and subsequent retention of products of metabolism being factors in the increased heat production has not been eliminated inasmuch as Peabody, Meyer and DuBois (11) have shown that occasionally there is an increase in the basal metabolism in cardio-renal cases with cardiac decompensation.

Another question of primary importance arises, namely, is it the medullary or cortical influence which is primarily concerned in the above mentioned disturbance of metabolism. All the evidence at present available indicates that the cortex is the important and the medulla the unimportant tissue as regards maintenance of life. Only those animals survive suprarenalectomy who have functionally active cortex. Epinephrin does not prolong life after suprarenalectomy, and further, the discharge of epinephrin may be nearly if not completely abolished without apparent injury to the animal. As has already been pointed out, if a portion of the cortex, or if only accessories are present, the rise of the metabolic rate may not occur. Also, if most of the cortex is crippled by freezing, leaving the greater part of the medulla intact, as determined histologically, a marked rise may occur. This evidence, although meager, points to the cortex both as the tissue necessary to life and to its being more intimately related to the increased heat production than the medulla. However, freezing experiments do not exclude the medulla as an important factor in this phenomenon since the nerves going to the glands are also frozen and many investigators have shown that the discharge of epinephrin is dependent upon intact nerves (12).

Finally there are many points of similarity between the symptom complex that results from suprarenal injury as above described in rabbits and exophthalmic goiter in man. This possible relationship will be presented in a separate paper. \*

#### CONCLUSIONS

1. Removing or crippling (by freezing) the suprarenal glands in rabbits causes a disturbance in metabolism, usually characterized by increased heat production and  $\text{CO}_2$  output.

2. This disturbance appears definitely related to the completeness of removal of the cortical function.

3. The symptom complex including both anatomical and physiological data which results from the destruction of the suprarenal function in rabbits resembles in many essential features the symptom complex of exophthalmic goiter.

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## INFLUENCE OF GLANDS WITH INTERNAL SECRETIONS ON THE RESPIRATORY EXCHANGE

### III. EFFECT OF SUPRARENAL INSUFFICIENCY (BY REMOVAL) IN THYROIDECTOMIZED RABBITS

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In a previous paper (1) it was shown that by removing or crippling the suprarenal glands in rabbits striking changes in the respiratory exchange resulted. These could be grouped under three headings as follows:

a. Rabbits that live indefinitely after removal or injury of the suprarenals with no appreciable alteration in the respiratory exchange.

b. Rabbits that show an increase in the respiratory exchange followed by a fall to or below normal, whether dying within 2 or 3 weeks or living on indefinitely.

c. Rabbits that show a fall in the metabolic rate, beginning within 48 hours after removal or injury of the glands and continuing to death.

The details of these groups in relation to the kind of injury and completeness of removal of the suprarenals are given in the following table.

TABLE I

SUPRARENAL GLANDS	GROUP I, NO RISE IN HEAT PRODUCTION	GROUP II, RISE IN HEAT PRODUCTION	GROUP III, FALL IN HEAT PRODUCTION
Frozen* .....	8	6	1
(a) Complete removal—no accessories found .....	1	9	1
(b) Complete removal—accessories found .....	1	8	2
(c) Incomplete removal .....	4	1	
Totals .....	14	24	4

Two (nos. 224 and 231) excluded on account of infection.

Possible causes of the increased heat production were discussed. It was pointed out that trauma, infection and injury to nerves could be eliminated as important factors and that the simplest explanation of the phenomena observed with the facts at present available was that the increased heat production was in part due to increased thyroid activity brought about by the removal of a regulatory and inhibitory influence normally exercised by the suprarenals.

Inconclusive evidence was presented indicating that the underlying factor in the increased heat production was removal or insufficiency of the cortex rather than of the medulla.

The experiments included in this paper were undertaken to obtain further data on the question whether the thyroid, as previously suggested, was an important factor in the increased heat production following suprarenalectomy. For this purpose the following procedures were carried out on six rabbits. 1, "Normal" heat production records (using the Haldane apparatus as described in a previous paper) were obtained over a period of 2 weeks; 2, the thyroid glands were removed as completely as possible, leaving the external parathyroids with undisturbed blood supplies and the heat production measured for the next 23 days when, 3, the suprarenals were removed and further measurements of the respiratory exchange continued until the animals either died or were sacrificed. The protocols follow:

*Protocol I.* Rabbit 266. Male—several skin wounds from recent fighting—poorly nourished.

1921.

- May 31. Began metabolic studies. Weight 1827 grams.
- June 8. Urea N. = 10.0; creatinin 1.2.<sup>1</sup>
- June 13. Under ether removed most of thyroid gland, enlarged hyperemic, histologically moderate hyperplasia. Urea N. = 11.4; creatinin 1.7.
- June 29. Opened widely large subcutaneous abscess on back and rump. Thyroidectomy wound completely healed.
- July 6. Weight 2076 grams. Under ether removed right and left suprarenal glands, both enlarged and together weigh 0.66 gram, containing 0.70 mgm. epinephrin.
- July 7. Dull, slow respirations, diarrhea.
- July 12. Losing weight rapidly, dull, but ate oats, cabbage and hay.
- July 14. Opened several other small subcutaneous abscesses in ischial region, suprarenalectomy wounds healed.
- July 20. Emaciation, asthenia, diarrhea with blood, died. Autopsy one hour after death. Weight 1665 grams. Markedly emaciated, large incompletely drained subcutaneous abscesses on lower back and ischial

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<sup>1</sup> Figures for urea N and for creatinin indicate mgm. per 100 cc. blood.



region. No definite thyroid tissue found, small hyperemic area on anterior wall of trachea about 0.5 cm. below cricoid, saved for sections. Histological examination showed it to be thyroid. Moderate amount of fat in subcutaneous tissue of neck. Thymus area fatty, active thymic tissue present. Lungs normal; heart very flabby and dilated; liver slightly reduced in size, dark brown; kidneys normal in appearance; suprarenalectomy wounds clean and healed; right and left suprarenal glands completely removed, no accessories found; spleen normal; pancreas not hyperemic; moderate amount of perirenal fat; testes reduced in size; rectum and straight gut

TABLE 2  
*Rabbit 266*

DATE	ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KG. PER HOUR	
1921		grams						
May 31	22.8	1827	2.885	3.845	97	10.11	2.77	
June 2	23.1	1827	2.790	3.570	93	9.69	2.65	
June 6	23.1	1806	2.680	3.700	100	9.51	2.63	
June 9	24.1	1823	2.720	3.665	98	9.56	2.62	
June 17	24.8	1915	2.115	2.835	98	7.40	1.93	June 13. Thyroidectomy
June 21	25.8	1969	1.955	2.590	96	6.86	1.74	
June 27	27.3	2047	2.240	3.030	99	7.84	1.92	
July 5	26.9	2076	2.165	2.940	99	7.61	1.83	
July 7	27.0	2008	2.300	2.600	82	7.79	1.94	July 6. R. and L. suprarenalectomy complete
July 10	28.0	1924	2.050	2.555	91	7.05	1.83	
July 12	26.8	1888	2.405	2.730	83	8.10	2.15	
July 14	27.2	1829	1.730	2.405	103	6.18	1.69	Figured on basis of 100 R.Q.
July 16	25.0	1792	2.100	2.525	87	7.22	2.01	
July 18	26.6	1678	1.380	1.480	78	4.61	1.37	

hyperemic, small hemorrhages in mucosa. Gastric mucosa intact. Death due to suprarenal insufficiency and extensive cutaneous abscesses from old bites and possibly somewhat delayed by thyroidectomy.

*Protocol II. Rabbit 267. Male, well nourished.*

1921.

May 31. Weight 2207 grams. Began metabolic studies.

June 3. Urea N = 13.1; creatinin 1.6.

June 13. Under ether removed most of thyroid gland. Urea N = 16.3; creatinin 1.7. Thyroid small, normal histologically.

- July 6. Under ether removed right and left suprarenal glands completely; together weigh 0.75 gram, containing 0.78 mgm. epinephrin.  
 July 12. Active, ate full ration, developing tendency to attack by biting and scratching when hand is put in cage.  
 July 15. Wounds healed, becoming vicious.  
 July 23. Getting weaker, not so active, eats sparingly of ration.

TABLE 3

*Rabbit 267*

DATE		ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KGM. PER HOUR	
1921			grams						
May	31	24.4	2207	3.030	3.720	89	10.45	2.37	
June	6	23.1	2222	2.965	3.620	87	10.35	2.33	
June	9	24.1	2243	3.010	3.705	90	10.32	2.30	
June	17	24.8	2269	2.605	3.160	88	8.96	1.97	June 13. Thyroidectomy.
June	22	26.0	2294	2.505	3.205	93	8.70	1.90	
June	27	27.3	2366	2.735	3.305	88	9.37	1.98	
July	5	26.9	2392	2.440	3.480	104	8.94	1.87	Figured on basis of 100 R.Q.
July	8	28.5	2298	2.245	2.710	88	7.68	1.67	July 6. R. and L. suprarenalectomy complete
July	10	28.0	2387	2.100	2.820	98	7.36	1.54	
July	12	26.0	2363	2.280	2.930	94	7.89	1.67	
July	14	27.2	2331	2.175	3.095	103	7.95	1.71	Figured on basis of 100 R.Q.
July	16	25.0	2318	2.270	3.215	105	8.26	1.78	Figured on basis of 100 R.Q.
July	18	26.6	2284	2.205	2.815	93	7.64	1.67	
July	20	25.0	2254	2.115	2.795	97	7.35	1.63	
July	22	25.8	2169	1.680	2.215	96	5.87	1.35	
July	25	28.7	2125	2.125	2.280	78	7.11	1.67	
July	28	29.2	2156	1.800	2.250	91	6.21	1.44	
August	1	23.0	2124	1.975	2.555	94	6.88	1.62	
August	4	21.9	2049	2.115	2.470	86	7.13	1.74	
August	6	24.2	2015	2.065	2.240	79	6.91	1.72	
August	8	24.6	1952	1.480	2.010	99	5.20	1.33	

July 29. Urea N = 24.5; creatinin 2.6.

July 30. Very dull, eats sparingly of oats and lettuce.

August 5. Urea N = 22.45; creatinin 2.5.

August 9. Very dull, weak, unable to hold head up; gave salt solution extract of two fresh rabbit's suprarenals intraperitoneally.

August 10. Has not eaten, progressively weaker and died at 6 p.m., autopsy at once, weight 1930 grams. No thyroid tissue found at site of thy-

roid lobes; both external parathyroids present and normal; thymus atrophic; moderate amount of fat at site; lungs normal; heart very flaccid and dilated; liver dark brown red, much reduced in size; both suprarenal glands completely removed, sites clean and healed, no accessories found, small clumps of yellowish material (suprarenal emulsion injected yesterday) in omentum; spleen small; pancreas not hyperemic; kidneys pale, no pitting; moderate amount of perirenal fat; testes atrophic; stomach and intestines nearly free of food; stomach contains about 10 cc. nearly clear secretion, no ulcers.

*Protocol III. Rabbit 269. Male, well nourished.*

1921.

- May 31. Weight 2434 grams. Began metabolic studies.  
June 6. Urea N = 15.4; creatinin 1.6.  
June 13. Under ether removed most of thyroid gland, firmly attached to and high on larynx, not enlarged. Urea N = 17.3; creatinin 1.9.  
June 28. Under ether removed right suprarenal gland completely, weight 0.15 gram. Urea N = 22.8; creatinin 1.9.  
July 6. Under ether removed left suprarenal completely, weight 0.24 gram containing 0.19 mgm. epinphrin, scanty perirenal fat visible.  
July 8. Eating well, active, soft stools.  
July 16. Suprarenalectomy wounds healed, strong, active.  
July 29. Urea N = 25.2; creatinin 2.1.  
August 6. In excellent condition, gaining weight.  
August 19. Urea N = 28.4; creatinin 2.35.  
August 30. Hearty, vigorous.  
September 2. Urea N = 25.2; creatinin 1.9.  
September 7. Weight 2705 grams. General appearance normal, strong, active. Sacrificed to terminate experiment. Autopsy at once. Regenerated fragment of very vascular thyroid 2 mm. in diameter on right side at site of ligature. Otherwise complete removal. Parathyroids normal; thymus apparently completely replaced by fat; left lung normal, right shows few patches of consolidation. Heart dilated, flaccid. Liver slightly smaller than normal, somewhat paler and a little tougher on section than normal. Both kidneys are normal. Spleen dark red, normal in size. Pancreas hyperemic. Right and left suprarenals completely removed. Five very minute accessory cortical masses were found—three on left and two on right side. None of the masses were over 0.5 mm. in diameter. On the fat of the right epididymis are two brownish-yellow masses approximately 2 mm. in diameter resembling suprarenal cortex. This was verified by histological examination. Testes normal. No enlargement of lymph glands. Abundant fat in all depositories. Stomach filled with food. Mucosa normal. Intestinal tract normal throughout.

*Protocol IV. Rabbit 270. Male, well nourished.*

1921

- May 31. Weight 2124 grams. Began metabolic studies.  
June 6. Urea N = 11.6; creatinin 1.7.

- July 6. Under ether removed right and left suprarenal glands completely; together weigh 0.75 gram, containing 0.78 mgm. epinephrin.  
 July 12. Active, ate full ration, developing tendency to attack by biting and scratching when hand is put in cage.  
 July 15. Wounds healed, becoming vicious.  
 July 23. Getting weaker, not so active, eats sparingly of ration.

TABLE 3  
*Rabbit 267*

DATE	ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KG. PER HOUR	
1921		grams						
May 31	24.4	2207	3.030	3.720	89	10.45	2.37	
June 6	23.1	2222	2.965	3.620	87	10.35	2.33	
June 9	24.1	2243	3.010	3.705	90	10.32	2.30	
June 17	24.8	2269	2.605	3.160	88	8.96	1.97	June 13. Thyroidectomy.
June 22	26.0	2294	2.505	3.205	93	8.70	1.90	
June 27	27.3	2366	2.735	3.305	88	9.37	1.98	
July 5	26.9	2392	2.440	3.480	104	8.94	1.87	Figured on basis of 100 R.Q.
July 8	28.5	2298	2.245	2.710	88	7.68	1.67	July 6. R. and L. suprarenalectomy complete
July 10	28.0	2387	2.100	2.820	98	7.36	1.54	
July 12	26.0	2363	2.280	2.930	94	7.89	1.67	
July 14	27.2	2331	2.175	3.095	103	7.95	1.71	Figured on basis of 100 R.Q.
July 16	25.0	2318	2.270	3.215	105	8.26	1.78	Figured on basis of 100 R.Q.
July 18	26.6	2284	2.205	2.815	93	7.64	1.67	
July 20	25.0	2254	2.115	2.795	97	7.35	1.63	
July 22	25.8	2169	1.680	2.215	96	5.87	1.35	
July 25	28.7	2125	2.125	2.280	78	7.11	1.67	
July 28	29.2	2156	1.800	2.250	91	6.21	1.44	
August 1	23.0	2124	1.975	2.555	94	6.88	1.62	
August 4	21.9	2049	2.115	2.470	86	7.13	1.74	
August 6	24.2	2015	2.065	2.240	79	6.91	1.72	
August 8	24.6	1952	1.480	2.010	99	5.20	1.33	

July 29. Urea N = 24.5; creatinin 2.6.

July 30. Very dull, eats sparingly of oats and lettuce.

August 5. Urea N = 22.45; creatinin 2.5.

August 9. Very dull, weak, unable to hold head up; gave salt solution extract of two fresh rabbit's suprarenals intraperitoneally.

August 10. Has not eaten, progressively weaker and died at 6 p.m., autopsy at once, weight 1930 grams. No thyroid tissue found at site of thy-

roid lobes; both external parathyroids present and normal; thymus atrophic; moderate amount of fat at site; lungs normal; heart very flaccid and dilated; liver dark brown red, much reduced in size; both suprarenal glands completely removed, sites clean and healed, no accessories found, small clumps of yellowish material (suprarenal emulsion injected yesterday) in omentum; spleen small; pancreas not hyperemic; kidneys pale, no pitting; moderate amount of perirenal fat; testes atrophic; stomach and intestines nearly free of food; stomach contains about 10 cc. nearly clear secretion, no ulcers.

*Protocol III. Rabbit 269. Male, well nourished.*

1921.

- May 31. Weight 2434 grams. Began metabolic studies.  
June 6. Urea N = 15.4; creatinin 1.6.  
June 13. Under ether removed most of thyroid gland, firmly attached to and high on larynx, not enlarged. Urea N = 17.3; creatinin 1.9.  
June 28. Under ether removed right suprarenal gland completely, weight 0.15 gram. Urea N = 22.8; creatinin 1.9.  
July 6. Under ether removed left suprarenal completely, weight 0.24 gram containing 0.19 mgm. epinphrin, scanty perirenal fat visible.  
July 8. Eating well, active, soft stools.  
July 16. Suprarenalectomy wounds healed, strong, active.  
July 29. Urea N = 25.2; creatinin 2.1.  
August 6. In excellent condition, gaining weight.  
August 19. Urea N = 28.4; creatinin 2.35.  
August 30. Hearty, vigorous.  
September 2. Urea N = 25.2; creatinin 1.9.  
September 7. Weight 2705 grams. General appearance normal, strong, active. Sacrificed to terminate experiment. Autopsy at once. Regenerated fragment of very vascular thyroid 2 mm. in diameter on right side at site of ligature. Otherwise complete removal. Parathyroids normal; thymus apparently completely replaced by fat; left lung normal, right shows few patches of consolidation. Heart dilated, flaccid. Liver slightly smaller than normal, somewhat paler and a little tougher on section than normal. Both kidneys are normal. Spleen dark red, normal in size. Pancreas hyperemic. Right and left suprarenals completely removed. Five very minute accessory cortical masses were found—three on left and two on right side. None of the masses were over 0.5 mm. in diameter. On the fat of the right epididymis are two brownish-yellow masses approximately 2 mm. in diameter resembling suprarenal cortex. This was verified by histological examination. Testes normal. No enlargement of lymph glands. Abundant fat in all depositories. Stomach filled with food. Mucosa normal. Intestinal tract normal throughout.

*Protocol IV. Rabbit 270. Male, well nourished.*

1921

- May 31. Weight 2124 grams. Began metabolic studies.  
June 6. Urea N = 11.6; creatinin 1.7.

TABLE 4

*Rabbit 269*

DATE		ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KG. PER HOUR	
1921			grams						
May	31	24.4	2434	2.640	3.480	96	9.22	1.89	
June	2	23.9	2479	2.985	4.145	102	10.65	2.16	Figured on basis of 100 R.Q.
June	6	23.4	2482	3.235	4.180	94	11.26	2.27	
June	9	24.8	2500	3.300	4.315	95	11.53	2.31	
June	17	25.3	2531	2.930	3.480	86	10.04	1.98	June 13. Thyroidectomy
June	22	28.0	2643	2.810	3.560	92	9.75	1.85	
June	27	29.1	2721	2.680	3.730	102	9.58	1.76	Figured on basis of 100 R.Q.
July	5	26.4	2676	2.620	3.465	97	9.11	1.70	June 28. R. suprarenalectomy complete
July	8	28.5	2688	2.660	3.315	91	9.15	1.70	July 6. L. suprarenalectomy complete
July	10	28.8	2582	2.625	3.150	88	8.93	1.73	
July	12	26.0	2606	2.680	3.560	97	9.36	1.80	
July	14	27.2	2606	2.565	3.720	105	9.56	1.83	Figured on basis of 100 R.Q.
July	16	25.0	2624	3.300	4.265	94	11.49	2.19	
July	18	26.6	2620	2.695	3.690	100	9.48	1.81	
July	20	25.0	2655	2.935	4.050	100	10.40	1.96	
July	22	24.4	2674	2.890	3.940	99	10.20	1.91	
July	25	28.1	2678	2.680	3.530	96	9.35	1.75	
July	28	29.2	2714	2.810	3.510	91	9.69	1.79	
August	1	23.0	2718	3.005	3.870	94	10.42	1.92	
August	8	24.9	2735	2.835	3.740	96	9.91	1.81	
August	12	26.2	2788	2.635	3.380	93	9.18	1.65	
August	16	24.2	2788	2.900	3.715	93	10.09	1.81	
August	19	24.4	2725	2.940	3.655	90	10.18	1.87	
August	23	26.6	2755	3.095	3.760	88	10.66	1.93	
August	30	25.7	2752	2.850	3.470	88	9.84	1.79	
September	6	28.0	2712	2.770	3.320	87	9.50	1.75	

June 13. Under ether removed most of thyroid gland, not enlarged. Urea N = 14.0; creatinin 1.8.

July 6. Under ether removed right and left suprarenal glands completely and together weigh 0.47 gram, containing 0.52 mgm. epinephrin.

July 12. Active, ate heartily of oats, hay and lettuce.

- July 18. Wounds healed and stitches removed.  
 July 26. Getting duller and weaker, eats very little.  
 July 29. Urea N = 27.3; creatinin 2.6.  
 July 30. Very dull, possibly has eaten some lettuce and oats.  
 August 1. Died this afternoon and autopsy at once. Small fragment of very hyperemic thyroid approximately 2 mm. in diameter on right side, near site of old stump ligature; thymus present, considerable thymic tissue visible; lungs normal; heart dilated and flaccid; liver markedly

TABLE 4  
*Rabbit 270*

DATE		ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KG. PER HOUR	
1921			gm.						
May	31	25.2	2124	2.670	3.560	97	9.36	2.21	
June	4	23.8	2256	3.285	4.275	95	11.42	2.53	
June	7	23.2	2260	3.090	4.115	97	10.82	2.39	
June	10	24.3	2305	3.400	3.840	82	11.50	2.50	
June	17	25.5	2372	2.905	3.535	88	10.02	2.11	June 13. Thyroidectomy
June	22	28.0	2474	2.915	3.665	92	10.03	2.03	
June	27	29.1	2560	2.905	3.780	94	10.18	1.99	
July	5	26.9	2531	2.985	4.080	99	10.56	2.09	
July	8	28.5	2472	2.740	3.300	88	9.36	1.89	July 6. R. and L. suprarenalectomy complete
July	10	28.8	2424	2.750	3.130	83	9.29	1.92	
July	12	26.2	2296	2.720	3.555	96	9.42	2.05	
July	14	27.2	2227	2.550	2.875	82	8.61	1.93	
July	16	26.9	2232	2.170	2.865	96	7.59	1.70	
July	18	26.6	2192	2.295	2.875	91	7.94	1.81	
July	20	25.0	2138	2.460	3.045	91	8.41	1.97	
July	22	24.4	2068	2.040	2.670	95	7.13	1.72	
July	25	28.1	2030	2.030	2.530	91	6.99	1.72	
July	28	29.2	1969	1.875	2.245	87	6.42	1.63	
August	1	23.0	1827	1.475	1.765	87	5.05	1.38	

reduced in size, dark brown red; kidneys small, dark red, surfaces smooth, no "pitting"; right and left suprarenals completely removed, no accessories found, there is a brownish subperitoneal discoloration over right psoas muscle for some distance below kidney, probably the remains of a slight extraperitoneal extravasation of blood at time of suprarenalectomy; spleen small; pancreas slightly hyperemic; stomach contains moderate amount of food, no ulcers; testes small; moderate amount of abdominal and subcutaneous fat.

*Protocol V. Rabbit 271. Male, well nourished.*

1921

May 31. Weight 1858 grams. Began metabolic studies.

June 6. Urea N = 21.0; creatinin 1.7.

June 13. Under ether removed most of thyroid gland, external parathyroids high and may have injured blood supply; thyroid enlarged, hyperemic and histologically moderate hyperplasia. Urea N = 12.5; creatinin 1.7.

TABLE 6

*Rabbit 271*

DATE	ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER EGM. PER HOUR	
1921		gm.						
May 31	25.2	1858	2.145	3.035	103	7.80	2.10	Figured on basis of 100 R. Q.
June 3	22.0	1913	2.800	3.780	99	9.79	2.56	
June 7	23.2	1901	2.750	3.920	104	10.07	2.65	Figured on basis of 100 R.Q.
June 10	24.3	1925	2.780	3.785	100	9.72	2.53	
June 17	24.0	2017	2.480	3.440	101	8.84	2.19	June 13. Thyroidectomy
June 21	28.9	2074	1.940	2.880	110	7.40	1.78	Figured on basis of 100 R.Q.
June 27	29.1	2103	2.370	2.960	91	8.17	1.94	Figured on basis of 100 R.Q.
July 5	26.4	2081	2.245	2.910	95	7.77	1.87	June 28. R. suprarenalectomy complete
July 7	27.0	2056	2.340	2.530	79	7.81	1.90	July 6. L. suprarenalectomy complete
July 10	28.0	2038	2.055	2.500	89	7.03	1.72	
July 12	26.8	2045	2.250	2.785	90	7.76	1.90	
July 14	28.5	1986	2.085	2.585	91	7.14	1.80	
July 16	26.9	1975	1.565	2.230	104	5.73	1.45	Figured on basis of 100 R.Q.
July 18	27.0	1947	1.875	2.225	86	6.42	1.65	
July 20	27.0	1877	1.270	1.915	111	4.92	1.31	Figured on basis of 100 R.Q.
July 22	24.4	1849	1.345	1.730	94	4.66	1.26	
July 25	28.1	1778	1.280	1.460	83	4.33	1.22	

June 28. Under ether removed right suprarenal completely, weight 0.17 gram, containing 0.18 mgm. epinephrin. Urea N = 20.3; creatinin 1.8.

July 6. Under ether removed left suprarenal gland completely, weight 0.24 gram, containing 0.24 mgm. epinephrin.

July 7. Dull, not eating, diarrhea.

July 9. Ate heartily of oats, cabbage and hay, diarrhea.

July 15. Dull, but eating well.

July 19. Adrenalectomy wounds completely healed, getting weaker, eating very little.



- July 24. Very dull, weak, soft stools, weight 1778 grams.  
 July 26. Died this afternoon and autopsy at once. No thyroid found, larynx saved for sections; thymus atrophic, but large mass of fat at site; lungs normal; heart dilated and flaccid; spleen small; right and left suprarenal glands completely removed, a possible accessory suprarenal on left renal vein; negative histologically; slight "pitting" of kidneys, the depressions being dark red in color; testes atrophic; abundant abdominal and subcutaneous fat; pancreas pale; stomach contains a fair amount of food, four small hemorrhages into mucosa of cardiac portion. Looks like typical suprarenal death.

*Protocol VI. Rabbit 272. Male, well nourished.*

1921

- June 1. Weight 1930 grams. Began metabolic studies.  
 June 6. Urea N = 15.4; creatinin 1.6.  
 June 13. Under ether removed most of thyroid gland, situated very high on larynx, slightly enlarged. Urea = 17.9; creatinin 1.7.  
 June 28. Under ether removed right suprarenal gland completely, weight 0.28 gram, containing 0.36 mgm. epinephrin. Urea N = 21.4; creatinin 1.8.  
 July 6. Under ether removed left suprarenal gland completely, weight 0.34 gram, containing 0.33 mgm. epinephrin. Abundant perirenal fat.  
 July 8. Eating well, very quiet.  
 July 16. Eats entire ration, quiet; suprarenalectomy wounds healed completely.  
 July 29. Urea N = 22.7; creatinin 1.9.  
 July 30. Looks normal, quiet, eats heartily.  
 July 19. Urea N. = 24.5.  
 September 1. Strong, healthy, normal-looking rabbit.  
 September 2. Urea N. = 25.2; creatinin 3.1.  
 September 7. Weight 2227 grams. Sacrificed to terminate experiment. Autopsy at once. There is a fragment of very vascular thyroid  $1.5 \times 2$  mm. on right side attached to larynx and a very thin veil-like fragment on anterior surface of trachea approximately  $1 \times 2$  mm. Parathyroids normal; thymus replaced by fat; both lungs normal; heart normal, muscle firm; liver normal in size and consistency; spleen small, pale; pancreas not hyperemic; right and left suprarenals completely removed, on the left side there is a small accessory suprarenal in the fat above and external to the kidney, also two other masses approximately  $1 \times 1$  mm. along spermatic vein near pelvic rim. On the right side there is a large accessory suprarenal 1.5 mm. in diameter on the peritoneum external and above the kidney, also another accessory suprarenal 1 mm. in diameter on the anterior surface of renal vein at its junction with the inferior vena cava. In all five large accessory suprarenals were found; kidneys are smooth, normal in size and color. There is an oval dark purplish encapsulated glandular mass roughly 3 mm. in length in the fat of each epididymis. They resemble accessory spleens in appearance but on histological examination were found to be extremely congested, hemorrhagic and hypertrophic accessory suprarenals. Stomach filled with food; mucosa normal as is also the intestine throughout; enormous deposits of fat in all depositories; bladder distended with clear urine.

TABLE 7  
*Rabbit 272*

DATE		ROOM TEMPERATURE	WEIGHT OF RABBIT	O <sub>2</sub> IN GRAMS, 2 HOURS	CO <sub>2</sub> IN GRAMS, 2 HOURS	R. Q.	TOTAL CALORIES, 2 HOURS	CALORIES PER KG. PER HOUR	
1921			gm.						
June	1	24.0	1930	2.890	3.470	87	9.92	2.57	
June	3	22.0	1972	3.010	3.610	87	10.32	2.62	
June	11	25.2	1981	3.070	3.840	91	10.60	2.68	
June	18	24.0	2060	2.455	3.245	96	8.60	2.09	June 13. Thyroidectomy
June	21	28.9	2099	2.345	3.030	96	8.03	1.91	
July	5	26.4	2134	2.500	3.070	90	8.55	2.00	June 28. R. suprarenal-ectomy complete
July	8	28.5	2121	2.100	2.735	89	7.69	1.81	July 6. L. suprarenalec- tomy complete
July	10	28.8	2158	2.355	3.240	100	8.32	1.93	
July	12	26.2	2150	2.425	3.360	101	8.63	2.01	Figured on basis of 100 R.Q.
July	14	28.5	2157	2.105	2.765	96	7.33	1.70	
July	16	26.9	2126	1.965	2.840	105	7.30	1.72	Figured on basis of 100 R.Q.
July	19	26.9	2145	2.270	3.055	98	7.97	1.86	
July	20	27.5	2146	2.040	2.895	103	7.44	1.73	Figured on basis of 100 R.Q.
July	22	24.4	2150	2.210	2.965	97	7.79	1.81	
July	25	28.1	2138	1.845	2.695	108	6.92	1.62	Figured on basis of 100 R.Q.
July	28	29.2	2167	2.155	2.955	100	7.59	1.75	
August	1	23.0	2168	1.860	2.845	113	7.31	1.69	Figured on basis of 100 R.Q.
August	8	24.6	2265	2.080	2.930	102	7.53	1.66	Figured on basis of 100 R.Q.
August	12	26.4	2286	2.300	2.945	93	7.99	1.75	
August	16	24.2	2244	2.050	2.805	101	7.21	1.61	Figured on basis of 100 R.Q.
August	19	24.4	2212	2.080	2.790	98	7.28	1.65	
August	23	23.0	2250	2.270	3.205	103	8.23	1.83	Figured on basis of 100 R.Q.
August	30	25.7	2309	2.225	2.950	97	7.76	1.68	
September	6	28.2	2232	2.270	2.530	82	7.58	1.70	Second 2 hours. Dis- carded first 2 hours on account of change of forceps.

Measurements of the respiratory exchange before thyroidectomy show the usual individual variations—the average per kilogram per hour being 2.13, 2.33, 2.41, 2.46, 2.62 and 2.67 calories for rabbits 269, 267, 270, 271, 272 and 266 respectively.

Following thyroidectomy the usual absolute decrease in the total heat production was obtained in five rabbits. It remained unchanged in one (270)<sup>2</sup> and the autopsy showed the thyroid had been incompletely removed. When the heat production was figured for calories per kilogram per hour a decrease was obtained in all experiments—being 31 per cent in rabbit 266, 20 per cent in rabbit 267, 20 per cent in rabbit 269, 13 per cent in rabbit 270, 24 per cent in rabbit 271 and 24 per cent in rabbit 272.

Following thyroidectomy gains in body weight varying from 200 to 400 grams and associated with rising respiratory quotients were observed. Twenty-three days after thyroidectomy the second suprarenal gland was removed (in three rabbits both suprarenals were removed at the same operation). Measurements of the respiratory exchange were continued on alternate days until the rabbit either died or further frequent measurements seemed unnecessary.

One rabbit died on the 14th, one on the 20th, one on the 26th, one on the 35th and two were sacrificed on the 63rd day after suprarenal-ectomy. The two rabbits that were sacrificed had apparently recovered and seemed normal in all respects except for the decreased heat production. Seven accessory suprarenals were found in each of these rabbits and there can be little doubt that their survival and recovery depended largely on this fact. No accessory suprarenals were found in the remaining four rabbits. The main suprarenal glands had been completely removed in all.

Thyroidectomy did not obviously modify the period of survival following suprarenalectomy. Loss of body weight likewise was as great as with

<sup>2</sup> The autopsy performed 49 days after thyroidectomy revealed a mass of vascular thyroid tissue 2 mm. in diameter on the right side at the site of the right lobe ligature. The thyroid was thought to have been completely removed and the present mass indicates regeneration. In two others, examined 80 days after thyroidectomy, considerable thyroid tissue was found. It is difficult to remove completely the thyroid in the average rabbit even after an enormous experience, the reason being that the anterior and superior border of the lobes are frequently firmly attached to the lower border of the larynx and in separating these attachments, fragments—possibly only a few cells—may be left, and on account of their great capacity for survival and growth appreciable masses often regenerate within a month.

suprarenalectomy alone although there has been more visible fat in the usual depositories. This probably is the result of the larger fat reserves in thyroidectomized rabbits. No thyroid tissue was found post-mortem (as determined both macroscopically and microscopically) in two, while in three regenerated masses of very vascular thyroid were present. In rabbit 266 a few thyroid follicles were found histologically.

The observation of particular importance in these experiments was the *absence* of a significant rise in heat production following suprarenalectomy in five of the six experiments (see tables 2 to 7). In suprarenalectomized rabbits with intact thyroids a rise of over 10 per cent was obtained in seventeen out of a total of twenty-two or 77 per cent. In no instance did the heat production after suprarenalectomy rise to the normal control level and in only one instance (rabbit 269) did it rise appreciably above the lowest level after thyroidectomy. In this instance the rise in heat production was typical. It began on the 4th day, reached its maximum on the 10th day following suprarenalectomy then gradually fell during the following 2 weeks but never to the low level reached following thyroidectomy alone. The animal recovered apparently completely except for the lowered heat production. When sacrificed several small accessory suprarenals together with a hyperplastic thyroid fragment 2 mm. in diameter were found. In another instance with recovery (rabbit 272) that did not show a post-suprarenalectomy rise in heat production, seven very large accessory suprarenals together with two hyperplastic fragments of thyroid were found when sacrificed. We believe the absence of the rise in heat production in this rabbit was dependent upon the large amount of accessory suprarenal cortex. These observations further illustrate the very small amount of functionally active suprarenal cortex necessary for the maintenance of health and how narrow the limits are even anatomically within which one must work in order to obtain a post-suprarenalectomy rise in heat production and survival of the animal. Also these experiments illustrate what small amounts of thyroid tissue under favorable conditions of nutrition may suffice to notably influence the heat production. Thus rabbit 270 showed only a very slight reduction in heat production following what was believed to be a complete thyroidectomy but the autopsy showed a very hyperplastic fragment of thyroid approximately 2 mm. in diameter. A comparison of the metabolism tables shows that the heat production in the three (269, 270 and 272) rabbits in which thyroid was found at autopsy was maintained on a much higher plane than in the two (267 and 271) where no thyroid

was found at autopsy. The few thyroid follicles found on microscopical examination in rabbit 266 probably had no measurable effect on its metabolism and therefore it should be grouped with rabbits 267 and 271.

Blood urea and creatinin were determined at intervals throughout the experiments. The data are given in the protocols.

Following suprarenalectomy the creatinin content of the blood showed a significant rise. The possible slight rise in the urea following thyroidectomy might be mentioned. These data could not be correlated with any gross renal lesions.

#### DISCUSSION

Partial destruction of the function of the suprarenal cortex in rabbits usually (77 per cent of our series) causes a rise in heat production and removal of the thyroid gland in our experiments has prevented it. These facts if confirmed would establish another thyroid-suprarenal interrelationship which, with the facts at present available, seems to depend on an antagonistic action of the thyroid and suprarenal cortex. The much discussed interrelationship of previous observers was assumed to depend on the mutual stimulating effects of the thyroid and chromaphil tissues. Thus, the original schema of Eppinger, Falta and Rudinger (2) assumed that the thyroid and the chromaphil tissues mutually aided each other. Asher and Flack (3) were the first to produce experimental evidence in support of this hypothesis by showing that a given dose of adrenalin produced a greater pressor effect after thyroid stimulation than before such stimulation or following removal of the thyroids. Levy (4) confirmed these observations. The so-called Asher-Goetsch (5) adrenalin sensitization test is a clinical diagnostic application of Asher and Flack's original observations. Later work by Peabody, Wearn, Clough, Tompkins and Sturgis (6), by Tompkins, Sturgis and Wearn (7), by Sandiford (8) in man and by Marine and Lenhart (9) in rabbits, has demonstrated that the thyroid is not necessary for this reaction although it seems established that a hyperfunctioning thyroid or even an intact normal gland increases the reaction. The work of Dreyer (10), Elliott (11) and later of Stewart and Rogoff (12) using more technical methods has shown that section of the nerves to the suprarenals reduces the epinephrin output below the level of detectability as determined by a very sensitive biological test without any apparent injury to the animal's health. This also indicates that thyroid stimulation by epinephrin is at least relatively unimportant. Since heat production

sufficient to maintain vegetative life can go on probably for months after complete removal of the thyroid and since adrenalin in excessive doses can stimulate heat production in the absence of the thyroid, it follows that there are many other more basic factors than either the thyroid or the suprarenal medulla involved in the maintenance of heat production. It is possible, however, that the thyroid gland and the chromaphil tissues through stimulation, and the thyroid gland and suprarenal cortex through antagonistic actions, may provide a means for maintaining a higher level of and for bringing about greater variations in heat production. Our observations that suprarenalectomy with intact thyroids causes a rise in the respiratory exchange and that thyroid removal prevents or greatly lessens this rise, if confirmed, would indicate that the rise is dependent upon an increased activity of the thyroid and that it is independent of any stimulating substance produced either in the cortex or medulla. The evidence further suggests that the suprarenal gland, and especially its cortex, exercises a regulatory, restraining or inhibitory control over the thyroid activity and the removal of this cortical influence acts as a much more powerful stimulus to thyroid activity than epinephrin.

This conception of thyroid control would explain the hyper-susceptibility of certain individuals to adrenalin as in part dependent upon a primary insufficiency of the suprarenal cortex and a thyroid-hyperactivity secondary to the cortical insufficiency. Similarly, the hyper-susceptibility to desiccated thyroid or thyroxin could be explained as in part dependent upon cortical insufficiency and normal or increased activity of the medulla. Likewise, the observations of R. G. Hoskins (13), E. R. Hoskins (14), Herring (15) and others that thyroid feeding causes enlargement of the suprarenal cortex and increased epinephrin store in the medulla; and of McCarrison (16) that inanition also causes enlargement of the suprarenal cortex and increased epinephrin store could be interpreted as attempts to depress thyroid function and tissue oxidation. Students of thyroid physiology have contended that the fundamental manifestations of exophthalmic goiter could not be explained on a thyroid hypothesis alone and that the alterations in thyroid structure and the increased thyroid function were secondary to and symptomatic of more important lesions elsewhere (17), (18). If the suprarenal cortex directly or indirectly exercises a restraining, regulatory or inhibitory control over the thyroid gland it will have introduced a conception of exophthalmic goiter which though differing widely from the still popular conception offers a possible explanation for many of its fundamental

manifestations. This conception would assume a weakness or exhaustion of the cortical function with unchanged, decreased or even increased medulla function as important underlying causes of the increased thyroid activity.

The possible importance of cortical insufficiency as a factor in the etiology of thyroid hypertrophies and hyperplasias of puberty, pregnancy, menstruation and menopause might also be suggested. One of the greatest arguments against a direct infectious theory of the origin of simple goiter has been the fact that beginning with the age of puberty human thyroid hypertrophy and hyperplasia is six or eight times more frequent in the female while in the lower animals or below puberty in man sex has no detectable influence on the incidence. It is known that bacterial toxins cause thyroid hyperplasia (19) and it is possible that this is an indirect action through the suprarenal cortex.

As to the means by which the suprarenal cortex normally exercises a control over thyroid activity only speculation is possible at present. Nothing definitely is known of the chemical activities of the cortex. It is possible that it elaborates some specific substance which regulates thyroid activity directly or which operates indirectly through control of the general tissue oxidations. In this connection one naturally turns to the "lipoids" which make up so large a part of the cortex and which many believe play an important rôle in the oxidation processes going on in all tissues. Lastly, while the thyroid-suprarenal cortex interrelationship has been emphasized in this paper, it is not believed that it is an isolated or independent one. On the contrary, there is abundant evidence that these tissues' functions must be intimately related directly or indirectly to many, probably all, other tissue functions both as regards accelerator and inhibitory actions and as regards simpler and more complex interrelations. We refer particularly to the suprarenal medulla, the interstitial cells of the sex glands, the thymus and lymphoid tissues, the hypophysis, the liver and the pancreas,

#### CONCLUSIONS

1. Partial but sufficient destruction of the function of the suprarenal cortex in rabbits with intact thyroids usually leads to an increased heat production.
2. Removal of the thyroid prevents or greatly lessens the increased heat production which usually follows partial destruction of the suprarenal cortex.

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manifestations. This conception would assume a weakness or exhaustion of the cortical function with unchanged, decreased or even increased medulla function as important underlying causes of the increased thyroid activity.

The possible importance of cortical insufficiency as a factor in the etiology of thyroid hypertrophies and hyperplasias of puberty, pregnancy, menstruation and menopause might also be suggested. One of the greatest arguments against a direct infectious theory of the origin of simple goiter has been the fact that beginning with the age of puberty human thyroid hypertrophy and hyperplasia is six or eight times more frequent in the female while in the lower animals or below puberty in man sex has no detectable influence on the incidence. It is known that bacterial toxins cause thyroid hyperplasia (19) and it is possible that this is an indirect action through the suprarenal cortex.

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#### CONCLUSIONS

1. Partial but sufficient destruction of the function of the suprarenal cortex in rabbits with intact thyroids usually leads to an increased heat production.
2. Removal of the thyroid prevents or greatly lessens the increased heat production which usually follows partial destruction of the suprarenal cortex.

3. While epinephrin in large amounts may stimulate the thyroid, it is believed that exhaustion or insufficiency of the regulatory, inhibitory and restraining effect of the cortical influence is a much more important cause of increased thyroid activity and increased tissue oxidations in rabbits.

4. Many other tissues and more complicated glandular interrelations may be involved—especially that closely related tissue, the interstitial cells of the sex glands.

5. The observations included in this paper may have an important bearing on the etiology of both exophthalmic goiter and simple goiter of puberty, pregnancy, menstruation and menopause.

*Note:* The respiratory exchange measurements were made by Miss Anna Cipra and Miss B. L. Lowe, to whom we wish to express our thanks.

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## INFLUENCE OF GLANDS WITH INTERNAL SECRETION ON THE RESPIRATORY EXCHANGE.

### IV. EFFECT OF SUPRARENAL INSUFFICIENCY IN CATS.\*†

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Marine and Baumann in 1921 demonstrated a significant and sustained increase in heat production in the majority of rabbits following suprarenalectomy or freezing the suprarenals (1). The importance of this type of reaction in general physiology and special pathology makes it desirable to ascertain whether this relationship between the suprarenal gland and basal metabolism is peculiar to some feature of organization in this species. The literature contains no satisfactory evidence on this point. Golyakowski, working with dogs and utilizing an undescribed method of ligation, studied the respiratory exchange (2). He reported an increase in  $\text{CO}_2$  and heat production in eight of twelve dogs. However, the importance to be attached to this observation is greatly diminished by the fact that the oxygen intake was not altered. On the other hand, Aub reported a decrease in heat production in three cats following suprarenalectomy but he did not investigate the effect of sublethal crippling of the suprarenals (3). No other references bearing in any way on this subject could be found.

The rabbit has relatively great normal temperature variations and it usually has accessory suprarenal masses, differing from the higher mammals in both points. The cat is a typical member of the latter group. The temperature is fairly constant and accessory

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suprarenals are rare. Therefore, total removal is followed by death usually within 2 to 5 days (4). Also in its diet and its fat metabolism the cat differs from the rabbit and resembles the organization of man. This point takes on special interest in view of the recent demonstration by Marine and Baumann that the thyroid function is essential for the increase in heat production during suprarenal insufficiency (5), taken in conjunction with the connection between the thyroid and the metabolism of fat pointed out by McCarrison (6). Therefore, in this report we wish to record the changes in heat production observed in cats following varying degrees of suprarenal injury produced by partial extirpation, vessel ligation, freezing, and various combinations of these procedures.

### *Methods.*

Cats were kept in the laboratory under uniform conditions of régime and diet for at least 3 weeks before determination of the respiratory exchange and they were run in the respiration chambers several times for training during this period. The gaseous metabolism was measured with the Haldane apparatus as modified by Marine and Lenhart (7). The room temperatures were kept relatively constant. The maximum variation (with the exception of October 5) was 19–24°C. with the mean of 21°C. Determinations were always made at least 15 hours after the last feeding; and a sufficient number of them over a period of at least 2 weeks was obtained to determine the normal range for the individual cat under the given conditions as regards season, food, state of nutrition, etc. About 10 per cent of the cats were rejected for this work because the control rates were too irregular. Those used were very quiet after becoming accustomed to the procedure, and frequently slept throughout the entire period in the metabolism chambers which was always 2 hours. Any periods in which the animal was restless were discarded.

Three methods were used in our attempts to cripple the suprarenal function:<sup>1</sup> (a) partial excision; (b) ligation of blood vessels; and (c) freezing.

*Partial Excision.*—This was the method first attempted as it would appear *a priori* to be the most exact means of producing varying

<sup>1</sup> All operations were performed under ether anesthesia.

degrees of suprarenal insufficiency. However, exactly the opposite was found to be the case. The leeway between the production of any effect and of a fatal insufficiency is extremely slight and uncontrollable. The removal of less than three-fourths of the suprarenal tissue produces no evidence of abnormality in heat production, while the result of removing more than this bears no necessary relationship to the anatomical amount remaining. Quite uncontrollable conditions, chiefly the blood supply of the remaining fragment, determine the outcome. By this method we were not able to produce any clinical change except the typical rapidly fatal symptom-complex of suprarenal suppression. This procedure was therefore abandoned.

*Ligation of Blood Vessels.*—For many years the fact has been known that occlusion of the lumbosuprarenal veins would produce marked histological changes in the suprarenal gland, particularly in the cortex (8). Hartman and Blatz, in 1919, reported clinical symptoms following ligation of the lumbosuprarenal veins which were suggestive of a functional suprarenal insufficiency as their basis (9).

Ligations of the suprarenal blood vessels were carried out in the following combinations: (a) right and left lumbosuprarenal veins; (b) left lumbosuprarenal vein with excision of the right suprarenal; (c) right and left lumbosuprarenal vein with mass ligation of the collateral renal-suprarenal vessels; and (d) left lumbosuprarenal vein with mass ligation of the collateral left suprarenal vessels and excision of the right suprarenal.

In ligating the lumbosuprarenal vein the peritoneum over it was slit just proximally and distally to the suprarenal gland and a silk ligature carried around the vein on an aneurysm needle without manipulating the gland or interfering with any of its nerve supply except those filaments that run in the sheath of the suprarenal vein. After ligation of the vein, congestion and swelling of the gland were observed to different degrees, the variation of which was extreme and unpredictable. Ligation by the same method in a series of animals gave entirely different results, depending on the collateral circulation which developed.

*Freezing.*—This method was developed by Marine and Baumann in their experiments to cripple the suprarenal glands in rabbits. They

pointed out the difficulties encountered in freezing the right gland and the relative ease on the left side. In the main the same situation prevails in cats except that the right suprarenal is somewhat more accessible, being usually less closely adherent to the vena cava. In some cases both glands were frozen, though more frequently the left was frozen and the right excised. Mobilizing the left suprarenal gland sufficiently to freeze it is very satisfactorily accomplished. The fatty areolar tissue is dissected back with the probe point for a distance of several millimeters so that the gland can easily be elevated with most of the nerves and minute blood vessels attached. A spray of ethyl chloride reaches all parts of the surface of the cortex. The duration of the freezing varies from 15 to 45 seconds, depending upon the degree of injury desired. There was difficulty encountered in obtaining ethyl chloride tubes having a spray sufficiently fine. Bengué tubes were the best available in this country at the time, and only about one in four of these was satisfactory. During the freezing the gland is blanched, but on thawing the circulation is seen to resume at once. To freeze the right suprarenal the lumbar approach is obligatory and the peritoneum is not opened, while for the left one either the lumbar or midline incision is satisfactory, and the suprarenal is reached transperitoneally. In either case the proper exposure of the suprarenal gland, effected by a fairly deep self-retaining retractor after the field is walled off and other structures are protected by sponges, is an important factor in controlling the degree of injury.

*Controls.*—Two types of control experiments were performed: (a) freezing tissue around the mobilized suprarenals, and (b) excision of one suprarenal gland.

(a) Two normal animals were subjected to operation in which both suprarenals were prepared as for freezing; the tissues about them were frozen but the glands themselves were not. This procedure included all the elements of shock, general trauma, and nerve and vascular injury that obtained when the glands were frozen, except for the actual injury to the cells of the suprarenal cortex.

(b) Five animals had one suprarenal excised, nothing being done at the time to the other gland.

In experiments in which thyroid function may be intimately concerned, the use of iodine for skin sterilization is contraindicated. Chemical sterilization of the skin by an alcoholic picric acid solution was the method used in these experiments.

*Presentation of Data.*

35 experiments were conducted on 24 cats in which the respiratory exchange was followed before and after operation, as follows: freezing, 10; ligation, 17; partial removal, 6; operative trauma, 2. The types of reaction to subtotal suprarenal insufficiency as observed in these cats may be roughly classified in three groups (Table I):

TABLE I.

Suprarenal glands.	Group I. No rise in heat production.		Group II. Rise in heat production.		Group III. Fall in heat production.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Frozen.....	1	10	6	60	3	30
Ligated.....	7	41	6	35	4	24
Partial removal and trauma (controls).....	7	88	0	0	1	12
Total.....	15	43	12	34	8	23

Group I. Those that live indefinitely and show no increase in basal metabolism.

Group II. Those that show a significant increase in basal metabolism (over 10 per cent).

Group III. Those that show a decrease in metabolism to a rapidly fatal termination.

There are variations in the reaction not specified in the above groups which will be referred to in the Discussion. No experiment has been considered to fall in Group II unless there was an increase of at least 10 per cent above the highest preoperative figure. The following six protocols have been selected as illustrative of the types of reaction observed.

*Group I; Protocol 1.*—Cat 10; adult, female (Table II). Aug. 29, 1921. Began metabolic determinations. Oct. 17. Under ether distally and proximally

ligated right and left lumbosuprarenal veins. Oct. 18. Active, eating well. Oct. 22. Normal in appearance. Oct. 24. Wound healed, stitches removed. Feb. 1, 1922. In stock; apparently in normal health.

*Group II; Protocol 2.*—Cat 7; adult, female (Table III). Sept. 2, 1921. Began metabolic determinations. Sept. 29. Under ether removed right suprarenal and froze the left. Oct. 1. Good appetite, alert, pupils dilated. Oct. 4. Marked diarrhea; eating very heartily (double ration). Oct. 6. Eating 150 gm. of milk and 150 gm. of meat each day and still seems hungry. Head feels

TABLE II.

*Cat 10.*

Date.	Weight.	O <sub>2</sub>	CO <sub>2</sub>	R.Q.	Total No. of calories.	No. of calories per kilo per hr.	Remarks.
1921	gm.	gm.	gm.				
Aug. 29	3,261	4.230	4.280	74	13.91	2.13	Control.
Sept. 2	3,138	3.805	3.825	73	12.58	2.00	"
" 14	3,148	4.485	4.520	73	14.86	2.36	"
" 16	3,154	3.655	3.955	79	12.21	1.94	"
" 30	3,198	3.730	4.090	80	12.49	1.97	"
Oct. 6	3,112	4.660	4.920	77	15.50	2.49	" (slightly restless).
" 10	2,972	4.065	4.250	76	13.53	2.28	"
" 13	2,818	3.860	4.050	76	12.89	2.29	"
Oct. 18	2,923	4.250	4.680	80	14.30	2.45	Oct. 17. Ligation of right and left suprarenal veins.
" 20	3,119	4.720	5.140	79	15.86	2.54	
" 22	3,181	4.400	4.750	79	14.66	2.30	
" 24	3,130	4.380	4.380	73	14.40	2.30	
" 26	3,204	4.900	5.430	81	16.43	2.56	
" 28	3,208	4.780	5.480	83	16.26	2.48	
" 31	3,185	4.540	4.870	78	15.18	2.38	
Nov. 3	3,328	4.480	5.130	83	15.22	2.29	
" 8	3,227	3.990	4.360	79	13.45	2.08	
" 11	3,060	4.230	4.310	74	14.02	2.29	
" 16	3,169	3.910	4.160	77	13.10	2.07	

warm. Oct. 27. Fur has become very glossy and smooth. Dec. 30. Sacrificed in good health.

*Protocol 3.*—Cat 18; three-quarters grown, female (Table IV). Sept. 26, 1921. Began metabolic determinations. Oct. 20. Under ether proximally and distally ligated right and left suprarenal veins. Oct. 22. Feels warm, eating well, active. Oct. 25. Not eating, very quiet. Oct. 26. Very weak, coughing occasionally. Oct. 27. Appetite returning. Nov. 18. Losing weight and strength, eating almost nothing, KI 25 mg. by mouth. Nov. 19. Very weak and



listless, scarcely holding up head; given emulsion of alcoholic extract residue from ox suprarenal cortex. Nov. 20. Very active and alert this morning, remarkable appetite, eating 100 gm. of meat without intermission; KI by mouth. Nov. 22. KI by mouth. Nov. 24. KI by mouth, gaining in weight, appearance improving. Nov. 25. KI 10 mg. Nov. 30. KI by mouth. Dec. 30. Sacrificed.

*Group III; Protocol 4.*—Cat 19; adult, female (Table V). Sept. 26, 1921. Began metabolic determinations. Oct. 7. KI 25 mg. by mouth. Oct. 29. Under

TABLE III.

Cat 7.

Date.	Weight.	O <sub>2</sub>	CO <sub>2</sub>	R.Q.	Total No. of calories.	No. of calories per kilo per hr.	Remarks.
1921	gm.	gm.	gm.				
Sept. 2	3,119	4.240	4.520	77	14.24	2.28	Control.
" 14	2,872	4.625	4.870	76	15.50	2.70	" (restless).
" 16	2,879	4.085	4.495	80	13.73	2.38	"
Sept. 30	2,891	3.910	4.250	79	13.12	2.28	Sept. 29. Right suprarenalec- tomy; left suprarenal frozen.
Oct. 2	2,784	4.410	4.480	74	14.57	2.62	
" 4	2,880	5.740	5.950	75	19.14	3.32	
" 6	3,028	5.710	5.950	76	18.94	3.13	
" 8	3,290	5.770	6.160	78	19.20	2.92	
" 10	3,242	4.920	5.080	75	16.33	2.52	
" 12	3,267	4.980	5.110	75	16.44	2.52	
" 15	3,405	5.010	5.200	75	16.72	2.46	
" 18	3,478	5.300	5.710	78	17.80	2.56	
" 20	3,675	5.760	6.250	79	19.29	2.62	
" 22	3,560	5.230	5.500	76	17.51	2.46	
" 24	3,506	4.900	5.010	74	16.29	2.32	
" 28	3,620	4.850	5.160	77	16.24	2.24	
Nov. 1	3,542	4.790	4.920	75	15.83	2.23	
" 8	3,202	3.670	3.930	78	12.25	1.91	
" 15	3,174	4.880	5.130	76	16.33	2.57	
" 21	3,444	4.560	4.670	74	15.18	2.20	

ether doubly ligated right and left suprarenal veins. Oct. 31. Very quiet and dopey in appearance. Nov. 2. Very weak, scarcely able to stand, feels cold, pupils dilated. Died during the night.

*Autopsy.*—Thyroid lobes very small, translucent, amber-yellow. Heart dilated, gray specks in pericardium; left suprarenal medulla is hemorrhagic, cortex necrotic. Three small, congested veins from posterior surface extending into perirenal fat and one into the renal vein. Right suprarenal is swollen but is not hemorrhagic,

TABLE IV.

*Cat 18.*

Date.	Weight.	O <sub>2</sub>	CO <sub>2</sub>	R.Q.	Total No. of calories.	No. of calories per kilo per hr.	Remarks.
<i>1921</i>	<i>gm.</i>	<i>gm.</i>	<i>gm.</i>				
Sept. 26	2,245	3.205	3.400	77	10.71	2.39	Control.
Oct. 5	2,203	3.810	4.160	79	12.84	2.91	" (temperature 16°C.; shivering).
" 10	2,047	2.585	2.770	78	8.63	2.11	Control.
" 13	1,951	3.115	3.365	79	10.43	2.67	"
Oct. 21	1,945	4.220	4.430	76	14.10	3.63	Oct. 20. Ligated right and left suprarenal veins.
" 23	1,937	3.770	4.090	79	12.62	3.26	
" 25	1,910	4.160	4.400	77	13.86	3.63	
" 27	1,937	3.430	3.710	78	11.56	2.99	
" 31	1,984	3.220	3.540	80	10.81	2.72	
Nov. 2	2,014	3.480	3.800	79	11.73	2.91	
" 4	2,001	3.730	3.980	78	12.41	3.10	
" 7	2,053	3.500	3.870	80	11.82	2.88	
" 9	2,147	4.200	4.640	80	14.18	3.30	
" 11	2,132	3.780	4.120	79	12.71	2.98	
" 14	2,156	3.480	3.920	82	11.74	2.72	
" 16	2,024	2.760	2.920	77	9.20	2.27	
" 18	1,894	2.190	2.390	80	7.29	1.92	
" 21	1,935	2.710	2.920	78	9.10	2.35	
" 22	1,988	3.340	3.820	83	11.33	2.85	
" 23	2,061	3.560	4.090	84	12.08	2.93	
" 25	2,110	3.190	3.550	81	10.74	2.54	
" 26	2,096	2.790	3.260	85	9.49	2.26	
" 28	2,228	3.670	4.250	84	12.49	2.80	
" 30	2,246	3.490	3.940	82	11.80	2.63	
Dec. 2	2,182	3.210	3.660	83	10.86	2.49	
" 5	2,077	2.530	2.760	79	8.52	2.05	
" 7	2,052	2.540	2.710	78	8.45	2.06	
" 9	2,022	2.450	2.670	79	8.24	2.04	
" 12	2,048	3.120	2.990	70	10.19	2.49	
" 14	2,090	2.730	3.120	83	9.26	2.21	
" 16	2,130	3.010	3.320	80	10.14	2.38	
" 20	2,214	3.240	3.770	85	10.98	2.48	

medulla appears intact grossly and microscopically, cortex yellowish white in color, microscopically necrotic. Abundant subcutaneous and abdominal fat. Other organs normal.

*Protocol 5.*—Cat 8; adult, female (Table VI). Aug. 29, 1921. Began metabolic studies. Sept. 29. Under ether removed right suprarenal and froze left. Sept. 30. Ate well. Oct. 1. Quiet and drowsy. Oct. 4. Very quiet, appears

TABLE V.

*Cat 19.*

Date.	Weight.	O <sub>2</sub>	CO <sub>2</sub>	R Q	Total No. of calories	No. of calories per kilo per hr.	Remarks.
1921	gm.	gm.	gm.				
Sept. 26	2,089	3.245	3.515	79	10.85	2.59	Control.
Oct. 3	2,158	2.800	3.200	83	9.49	2.20	"
" 6	2,125	2.830	3.260	84	9.58	2.25	"
" 11	2,148	2.560	2.800	80	8.55	1.99	"
" 14	2,264	2.730	3.270	87	9.35	2.07	"
" 19	2,289	3.240	3.550	80	10.85	2.37	"
" 21	2,303	3.450	3.710	78	11.58	2.51	"
" 25	2,152	2.600	2.760	77	8.69	2.02	"
Oct. 31	2,040	2.410	2.380	72	7.91	1.94	Oct. 29. Ligated right and left suprarenal veins.
Nov. 2	1,938	1.150	1.350	85	3.93	1.01	Nov. 3. Died.

TABLE VI.

*Cat 8.*

Date.	Weight.	O <sub>2</sub>	CO <sub>2</sub>	R.Q.	Total No. of calories	No. of calories per kilo per hr.	Remarks.
1921	gm.	gm.	gm.				
Aug. 29	2,412	4.135	4.320	76	13.75	2.85	Control.
Sept. 2	2,394	4.210	4.285	74	13.93	2.91	"
" 14	2,599	4.180	4.540	79	14.01	2.70	"
" 16	2,581	4.440	4.700	77	14.80	2.87	"
Sept. 30	2,719	3.530	3.980	82	11.92	2.19	Sept. 29. Right suprarenalectomy; left suprarenal frozen.
Oct. 2	2,649	4.400	4.510	75	14.51	2.74	
" 3	2,594	4.450	4.720	77	14.87	2.87	
" 6	2,502	3.080	3.240	77	10.21	2.04	
" 8	2,440	2.050	2.310	82	6.92	1.42	

dopey, alopecia, refuses meat, took 130 cc. of milk. Oct. 6. Lactose added to the milk; eating very little now. Oct. 7. Extremely weak. Lactose and milk 20 cc. by pipette. Oct. 8, p.m. Died.

*Autopsy.*—Abdominal and subcutaneous fat well preserved. Heart, normal color; heart's blood not coagulated. Right suprarenal absent; left embedded in omental adhesions, shows marked areas of necrosis in the cortex, medulla normal histologically. Stomach empty. Numerous erosions and hemorrhagic areas in mucous membrane.

*Control. Protocol 6.*—Cat 25; adult, male (Table VII). Oct. 28, 1921. Began metabolic observations. Nov. 5. KI 25 mg. by mouth. Nov. 8. Under ether mobilized both suprarenals and froze the tissue around them including blood vessels and nerves. Nov. 9. Normal appearance, eating well. Nov. 13. Normal behavior, marked dermatitis over shaved areas. Nov. 22. Wounds completely healed. Cat appears normal in every way.

TABLE VII.

*Cat 25.*

Date.	Weight.	O <sub>2</sub>	CO <sub>2</sub>	R.Q.	Total No. of calories.	No. of calories per kilo per hr.	Remarks.
1921.	gm.	gm.	gm.				
Oct. 28	2,589	3.790	3.780	73	12.43	2.40	Control.
" 31	2,683	4.710	4.750	73	15.62	2.91	"
Nov. 3	2,880	3.990	4.630	84	13.61	2.36	"
" 8	2,955	5.280	5.850	81	17.70	2.99	"
Nov. 9	2,785	4.540	4.640	74	15.09	2.71	Nov. 8. Control freezing operation.
" 11	2,618	3.780	3.960	76	12.60	2.41	
" 13	2,612	4.470	4.870	79	15.03	2.88	Marked dermatitis.
" 15	2,570	3.600	4.000	81	12.10	2.35	
" 17	2,522	3.400	3.790	81	11.46	2.27	
" 19	2,562	3.500	3.710	77	11.69	2.28	
" 21	2,574	3.780	4.100	79	12.65	2.46	
" 23	2,571	3.530	3.920	81	11.86	2.31	
" 26	2,619	3.800	4.260	82	12.82	2.45	
" 30	2,888	4.870	5.030	75	16.18	2.80	
Dec. 13	2,834	3.900	4.600	86	13.28	2.34	

*Group I.*—In this group the animals survive indefinitely and there is no increase in heat production of over 10 per cent. Eight, or 30 per cent of the twenty-seven experiments following freezing or ligation, presented this type of response to operation. These usually showed no noteworthy symptoms. Within 24 hours they had regained a normal appetite and behavior. In two cases there was a decrease in heat production lasting 2 weeks or more, not leading

to the death of the animal and with a subsequent return to the normal rate. Examination of the condition of the suprarenals either at autopsy or at a subsequent operation showed large areas of uninjured cortex, on both gross and microscopic examination. The medulla appeared quite normal. It is worthy of note that only one cat out of a total of ten, in which the suprarenals were frozen, fell in this group, and in this one the dissection of the gland for freezing was unsatisfactory on account of an excessive number of collateral blood vessels—a result of a previous ligation; while following vessel ligation, seven of seventeen showed no significant change in heat production. In the latter there was a well developed collateral circulation to the renal vein, the perirenal vein, and the diaphragm.

Protocol 1 illustrates this type of reaction. Eight determinations of the basal metabolism had been made over a period of 45 days, with a maximum variation of + 14 per cent and - 11 per cent from the average of 2.18 calories per kilo per hour. Both suprarenal veins were ligated proximally and distally to the suprarenal gland. Following this the gaseous metabolism was determined eleven times in 30 days—every other day for the first 2 weeks after operation. At no time was there a significant departure from the preoperative range, the maximum increase being 3 per cent above the highest normal figure.

*Group II.*—This group includes those cats whose heat production following suprarenal injury is increased at least 10 per cent above the highest preoperative figure. Twelve, or 44 per cent of the twenty-seven freezing or ligation experiments, showed this type of reaction. The increase varied from 18 to 44 per cent above the preoperative average and from 10 to 30 per cent above the highest preoperative figure. With one exception the rise in basal metabolism lasted from 9 to 38 days before again reaching the preoperative level. The increase in heat production was absolute as well as relative and in every case the cats survived the effect of suprarenal insufficiency indefinitely.

Coincident with the increased basal metabolism there were clinical manifestations of improved nutrition. Similar manifestations have been reported by Marine and Baumann in rabbits. The surface temperature seemed increased; the hair, which was shaggy in-

mediately after operation, became very sleek; and the appetite was often greatly increased. In spite of a food intake of double the normal amount the weight frequently was maintained at a level below its preoperative normal, though in some cases the cat gained tremendously in weight. Diarrhea was frequently observed, usually occurring at the height of the increase in heat production. Respiration was increased in rate and depth and at times there was a marked change in attitude and behavior, alertness and restlessness being observed.

Protocols 2 and 3 show typical examples of this type of reaction after freezing and ligation respectively. Cat 7 had the right suprarenal removed and the left frozen. The heat production was increased 36 per cent, reaching its maximum on the 5th day after operation and being maintained above the preoperative average for 20 days. The appetite was greatly increased and the cat gained 900 gm. in weight during this period of increased heat production, even gaining in weight when its basal metabolism was + 30 per cent. The total heat production also was increased by 30 per cent even before this gain in weight occurred. Diarrhea was noted on the 5th day after operation. The wounds healed promptly and the fur became very smooth.

Following this phase of increased heat production a slight depression averaging 10 per cent below the normal usually occurs, lasting from 1 to 4 weeks. That this may be partly due to an exhaustion of the thyroid gland is suggested by two facts. Potassium iodide given in two cases during this period of depression was followed by a prompt return to the normal level. And in several instances the thyroid gland was found 30 days after saturation with potassium iodide to be markedly hyperplastic in cats which had shown an increased basal metabolism after suprarenal crippling. At the time of being sacrificed the heat production had become subnormal. In control animals no such rapid exhaustion of the thyroid was observed.

Cat 18 showed an increase in heat production reaching the maximum of 44 per cent on the 1st and 5th days after ligation of both suprarenal veins. 2 days after operation it had regained its appetite and activity; however, by the 5th day after the operation it had become very inactive, was weak, and had lost its appetite. Its general

condition gradually improved; the basal metabolism remained elevated for 25 days, on the 20th day after the operation being + 40 per cent. At this time the animal lost its appetite and became very asthenic, rapidly losing weight; the heat production fell to 20 per cent below the preoperative figure. KI was given on November 18; on November 19 it ate less than 10 gm. of meat and did not hold its head up. Emulsion of suprarenal cortex extract was given by pipette. On November 20 the animal was very active, running and jumping, and when given food ate 100 gm. of meat without pause. The basal metabolism rose continuously for 3 days to a point above the preoperative range, it then became subnormal for a week, after which it resumed the original level. At autopsy the right suprarenal was found markedly atrophied; from the left there had developed a collateral circulation to the renal vein and the perirenal tissue. Colloid had disappeared almost completely from the thyroid vesicles and the epithelium was hypertrophic in spite of the fact that the cat had received potassium iodide 30 days previously in several doses.

*Group III.*—In this group the metabolism decreases slowly or rapidly till death. Seven, or 26 per cent of the twenty-seven animals, reacted in this way after freezing or ligation. The decrease in metabolism is on the average about 25 per cent. In the fulminating cases the picture is exactly like that after excision of both suprarenals (10), and the animal dies in 2 to 5 days. Two of this group lived 9 and 13 days respectively.

Histological examination of the suprarenal glands showed in each case marked injury to the suprarenal cortex. After freezing, the medulla had quite a normal appearance except for some congestion; its cells maintained their chromophilic properties. After ligation there was often very extensive hemorrhage into the medulla, though in some cases it remained entirely uninvolved. But the cortex always showed extensive necrosis in the animals of this group after either freezing or ligation. In some instances the entire cortex appeared to be necrotic, in others some areas of cortical cells staining fairly normally were found.

One cat in which fully seven-eighths of the suprarenal substance was excised reacted in this manner, showing marked reduction in heat production, and died  $2\frac{1}{2}$  days after operation. No viable supra-

renal cells could be found, and the vein leading from this remnant was completely thrombosed.

Protocols 4 and 5 are illustrative of this type of reaction. Cat 19 showed a decrease of 54 per cent 4 days after ligation of both suprarenal veins, and was unable to walk. It died the following night. Autopsy revealed hemorrhage into the medulla of the left suprarenal and marked necrosis in the cortex. Three small congested veins extended to the perirenal fat and one to the renal vein. The right suprarenal showed no hemorrhage into the medulla, which seemed normal, while the cortex showed large areas of necrosis. Cat 8 lived 9 days after excision of the right suprarenal and freezing of the left. The day after operation the heat production was 22 per cent below normal, it then rose on the 3rd and 4th days after the operation to the upper part of its normal range, thereafter falling sharply to 50 per cent below normal on the 9th day, and death occurred that night. There was increasing weakness so that on the 8th day the cat could not stand and anorexia was marked, though for the first 5 days it ate over 100 gm. of milk and some meat each day. Autopsy showed well preserved fat stores, right suprarenal absent, left suprarenal cortex with large areas of necrosis, and medulla with normal staining properties.

The animals suffering from a fatal suprarenal insufficiency, though living over a week, give definite evidence of cardiac weakness. The heart rate may become irregular, the mucous membranes are somewhat cyanotic, and the animal goes into collapse on slight exertion, which speaks strongly for a marked diminution in its cardiac reserve. At autopsy the heart is somewhat dilated and the musculature, especially of the right ventricle, is flabby.

*Controls.*—In the two cats in which both glands were mobilized and the tissues about the glands were frozen, the heat production after operation showed no increase. Also the five animals in which one suprarenal was removed showed no increase of 10 per cent above the preoperative level. That these animals could, however, show the typical rise in basal metabolism was demonstrated in three of these five cats by either a previous or subsequent operation.



## DISCUSSION.

The difference in reaction to suprarenal insufficiency in cats and rabbits, as reported in the literature, seems now to be cleared up. The previous failure to observe the characteristic increase in heat production in cats was due to the masking of this by the more profound effect of entire suppression of suprarenal function. In the six cases in which death resulted within a week from the suprarenal insufficiency, the heat production was invariably found to be continuously diminished, while in the two in which the suprarenal injury caused death, though the animal lived over a week, heat production in one case on the 4th day reached its highest preoperative level, and in the other case on the 5th day exceeded it, being followed in each case by a fall to death. Marine and Baumann observed in a small percentage of rabbits, also, this decrease in heat production to a rapidly fatal termination, and in them no accessory suprarenals could be found. It seems established then that when the suprarenal insufficiency approaches closely the suppression of suprarenal function heat production falls and death rapidly ensues. This is apparently due to the fact that the suprarenal glands, either by addition or subtraction, influence the reactive medium of the body in some manner essential to the continuance of vital metabolic processes.

Suprarenal injury less severe than the above causes in the majority of cats a profound effect upon the calorific mechanism, characterized by a significant increase in heat production. Of the twenty cats indefinitely surviving the suprarenal injury, twelve, or 60 per cent, showed this rise in basal metabolism, while of the control seven experiments involving all the elements of traumatization and manipulation of the suprarenals without serious damage to the glands, in none did the basal metabolism vary from its normal range by 10 per cent. In every case evidence of an increase in heat production was present in the 1st week, though the maximum frequently was not reached until later—24 days after operation in one instance. The rise lasted on the average 18 days before again reaching the preoperative base-line.

The secondary waves in the heat production curve mentioned by Golyakowski as occurring in dogs, and by Marine and Baumann in

rabbits, were very well marked in several instances. Cat 18 illustrates this phenomenon, one peak being in the 1st week after operation and another in the 3rd week.

After a period of suprarenal insufficiency associated with a significant rise in heat production there is usually a fall to 10 per cent or more below the base-line. That this is not altogether the effect of long training is shown by the fact that if it is followed sufficiently long the normal rate is resumed. This phenomenon resembles the period of hypothermia which is frequently seen in the convalescence from any prolonged fever. That thyroid exhaustion may be partly responsible for it is suggested by the effects of KI and by the rapid production of hyperplasia of the thyroid in these animals.

Of the three methods for producing suprarenal insufficiency in cats, partial excision was entirely unsatisfactory. Vein ligation gave good results in some cases but the collateral circulation was a dominant factor in the result which could not be predicted or controlled. In our hands freezing offered the most satisfactory means of controlling suprarenal injury.

In addition to the effect on heat production there are clinical symptoms, some of which can be readily correlated with it. Increased appetite, which may or may not be associated with a gain in weight, sleekness of fur, and rapidity of wound healing are nutritional manifestations which can be readily explained on the basis of thyroid function. There are other phenomena, however, which suggest vastly wider interrelationships between the suprarenal gland and the body tissues. In fatal suprarenal insufficiency gastric ulcer was frequently observed in this series in confirmation of the observations of other workers (11). Also symptoms of disturbed gastrointestinal function, most often manifest as diarrhea, were usually evident during the period of suprarenal insufficiency, most frequently observed at the time of maximal increase in basal metabolism. In one case diarrhea with numerous small blood clots was noted. Furthermore, the profound asthenia of the animals developing in the cases of fatal suprarenal insufficiency bespeaks a fundamental function of the suprarenal in relation to some part of the nerve-muscle motor mechanism. That this is not due merely to restriction of food intake was shown by the two cats which survived a fatal in-

sufficiency for over a week. In both cases operative recovery was prompt but a secondary profound weakness manifested itself about the 4th day which was well in advance of the stage of marked reduction in food intake. Cat 8, for example, was so weak, a week after operation that it could not walk on a flat surface, yet rough measurement showed the food intake up to this time to be 75 per cent of the caloric requirement of the animal. Rapid depletion of the glycogen stores have been demonstrated by previous observers (12). And other metabolic disturbances apart from the mobilization and use of fat were suggested by the rapidity of emaciation and the extreme degree to which it may be carried without exhaustion of the fat depots. Cat 12, for example, lost one-fifth of the body weight in 13 days, yet had abundant subcutaneous and mesenteric fat at autopsy. Extensive studies of the protein and especially of the water metabolism would be necessary to clear up this phenomenon.

A great mass of literature has sprung up about clinical suprarenal insufficiency, all of it vague, indefinite, and, up to the present, without any scientific support in fact (4), as there has been no method of differentiating the degrees of sublethal suprarenal insufficiency. Comparative measurements of heat production in the presence of an iodized thyroid may possibly offer a means of following to some degree the various phases of insufficiency of the suprarenal cortex. This work with cats, as well as that of Marine and Baumann with rabbits, shows that the partial suprarenal cortex insufficiencies produced experimentally are transitory and that compensation takes place rapidly or the animal dies. Therefore, one would not expect to demonstrate a suprarenal insufficiency in animals that have survived the injury for months.

Further evidence of the importance of the cortex as opposed to the medulla in influencing essential tissue functions is indirectly afforded by these experiments. In all cases in which death ensued from the suprarenal insufficiency, whether induced by freezing or ligation, marked damage to the cortex was evident, while the medulla usually retained its normal appearance grossly and microscopically. Even though secretion of epinephrine is possibly suppressed by freezing, vessel ligation leaves the nerve supply which controls this secretion, for the most part intact. There is a path for its discharge—

a definite collateral circulation between the suprarenal medulla and the perirenal tissue having been reported by Cow in 1914 (13) after ligation of the suprarenal vein proximally and distally to the gland. The collateral venous circulation of the suprarenal becomes markedly increased if the animal survives. These enlarged veins can readily be traced to the perirenal tissue, not infrequently to the diaphragm, and usually one or two directly to the renal vein. If it could be shown that under these conditions epinephrine was still discharged, it would necessarily follow that this agent played no essential part in the increased heat production.

It is impossible to study the syndrome of suprarenal insufficiency in cats without being impressed by the points of similarity between it and some of the outstanding features of Graves' disease. The most prominent single phenomenon in each is a significant increase in heat production. Each has a phase of asthenia and exhaustion, with evidence of severe cardiac damage. Diarrhea and nutritional and weight changes are common to each. Hyperplasia of the thyroid is produced in each and is characteristic of neither. Marine and Baumann have shown that the thyroid is indispensable for the increased heat production following suprarenal injury in rabbits but not for the asthenia and fatal termination. And, finally, that rather unusual form of Graves' disease running a rapidly fatal course in a very few weeks with severe asthenia, prostration, and coma bears a striking resemblance to the effect of fatal suprarenal insufficiency when death is postponed for several days.

#### CONCLUSIONS.

1. Severe and sufficient non-fatal injury to the suprarenal cortex by freezing or by ligation in cats causes a significant and prolonged increase in heat production.
2. Lethal injury to the suprarenals by freezing, ligation, or partial excision in cats causes a fall in heat production.
3. Insufficient injury to the suprarenals by freezing, ligation, or partial excision in cats produces no significant alteration in heat production.
4. Further evidence of a close thyroid-suprarenal cortex interrelationship is indicated by the rapidity of thyroid hyperplasia and by the effects of KI after suprarenal crippling.

I wish to express my appreciation for the continuous advice and interest of Dr. David Marine throughout this investigation.

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## INFLUENCE OF GLANDS WITH INTERNAL SECRETIONS ON THE RESPIRATORY EXCHANGE.

### V. FURTHER OBSERVATIONS ON THE EFFECT OF SUPRARENAL INSUFFICIENCY (BY REMOVAL) IN THYROIDECTOMIZED RABBITS.

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It has been shown by Golyakowski<sup>1</sup> on dogs, by Marine and Baumann<sup>2</sup> on rabbits, and by Scott<sup>3</sup> on cats, that severe but sublethal crippling of the suprarenal function by vessel ligation, by freezing or by partial removal\* with intact iodine containing thyroids usually leads to a prolonged increase in heat production. This increase in heat production usually begins within six days, and lasts from a week to several months falling gradually to or below the normal level. In a recent paper<sup>4</sup> we presented six experiments on rabbits showing that when the thyroid gland was removed and the respiratory exchange allowed to fall to the myxedema level prior to crippling the function of the suprarenals, this increase in heat production either did not occur or was greatly lessened. These findings, we believed, showed that the thyroid gland by reason of its iodine containing hormone was necessary for the reaction of increased heat production following suprarenal injury. Further, these experiments suggested another thyroid—suprarenal interrelationship in addition to the chromophil tissue (epinephrin) — thyroid interrelation. The latter, since Asher

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\* As pointed out in previous papers, accessory cortical tissue is probably present in all rabbits and is readily demonstrated in about 70 per cent. of rabbits. On account of this fact, one can obtain a more complete gradation of partial suprarenalectomies by complete removal of the main glands, than by attempting to leave a portion of the main glands intact. The accuracy of this statement is strikingly illustrated in the series of rabbits reported in this paper: (See Table X). In cats this method is not applicable because accessory cortical tissue occurs too rarely. While, theoretically, it should be possible to obtain the desired sublethal suprarenal insufficiency in this animal (cat) by partial removal of the main glands, practically, its accomplishment would be an accident because (1) the amount of active tissue necessary for apparently normal life is very small and probably variable, and (2) the impossibility of preserving unimpaired the blood supply or of estimating the functional capacity of the unremoved fragment.

and Flack's work, is believed to be due in part to a direct stimulating effect of epinephrin on the thyroid gland through its sympathetic nervous mechanism. The nature of the former reaction is still unknown. As a working hypothesis we suggested that the suprarenal cortex, in addition to other functions, normally exercised a regulatory or inhibitory control over thyroid activity, and when this control was sufficiently crippled as a result of severe physical injury, the thyroid automatically responded with increased activity resulting in increased heat production, if sufficient thyroxin were discharged during this increased activity.

The purpose of this paper is to present in detail nine additional experiments on rabbits again showing that thyroidec-tomy prevents or greatly diminishes the rise in the respiratory exchange which usually follows severe bilateral but sublethal injury to the suprarenal glands with intact thyroids.

The protocols follow:

Protocol 1. Rabbit 283. Female — adult gray.

Sept. 9, 1921. Began metabolic studies.

Nov. 8. Under ether removed spleen.

Jan. 11, 1922. Under ether removed most of R and L thyroid lobes (slightly enlarged).

Mch. 7. Under ether removed R suprarenal gland (much enlarged).

Mch. 28. Under ether removed L suprarenal gland (markedly enlarged). Kidneys normal; very little abdominal fat.

Apr. 10. Has shown no evidence of suprarenal removal. Active, hearty and strong.

May 12. Normal in behavior. Being used for antibody work.

July 8. Under ether removed R and L ovaries (not notably enlarged, yellowish); no accessories seen.

July 14. Weight 2786 gm., has shown no symptoms since ovariectomy, wound healed, rabbit strong and hearty. Killed. Autopsy at once. A large, very vascular mass of thyroid at site of R ligature, 3 x 3 x 1 mm., no other thyroid found. Paras small; thymus atrophic, no visible lymphoid tissue and very little fat in area. Lungs normal, save for area emphysema along anterior border of left upper lobe. Heart small and normal in color; liver normal; spleen absent; pancreas hyperemic. R and L suprarenals absent, no accessories found in region. There is a large 3 mm. bright yellow (necrotic) accessory in R ovariectomy stump; also a 2 mm. vascular accessory suprarenal in L ovariectomy stump. Kidneys small and normal. Stomach distended with food, mucosa normal; very little abdominal or subcutaneous fat; mammary glands involuted.



DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R Q.	Total Calories, 2 hours	Calories per kgm. per hr.	Behavior of Animal	REMARKS
1921									
Sept. 13	25.2	2758	3.555	4.295	88	12.18	2.21	Quiet	
" 15	24.0	2740	3.670	4.380	87	12.53	2.29	"	
" 19	21.2	2788	3.735	4.420	86	12.76	2.29	"	
Nov. 6	21.2	2567	3.030	3.730	90	10.39	2.02	"	
" 10	22.0	2548	3.840	5.160	98	13.46	2.64	"	
" 12	22.0	2584	3.700	4.810	95	12.85	2.49	"	
" 16	22.8	2614	3.230	4.010	90	11.17	2.14	"	
" 18	25.0	2626	3.100	3.740	88	10.60	2.02	Mkd snuffles	
" 22	21.0	2632	3.400	4.170	89	11.72	2.23	Restless	
1922									
Jan. 5	22.0	2816	3.890	4.790	90	13.34	2.37	Quiet	
" 20	21.5	2836	3.840	5.290	100	13.59	2.40	"	
" 26	20.8	2786	4.370	4.680	78	14.59	2.62	"	
" 30	23.5	2883	4.410	5.240	86	15.12	2.62	Restless	
Feb. 3	21.2	2962	3.510	4.540	94	12.23	2.06	"	Jan. 31 Thyroid-ectomy
" 6	22.5	3082	3.470	4.910	103	12.61	2.05	Quiet	
" 11	21.6	3153	4.450	5.930	97	15.59	2.47	"	
" 16	18.0	3207	4.410	5.970	98	15.58	2.43	Restless	
" 23	24.0	3286	3.570	4.400	90	12.25	1.86	"	
Mch. 2	23.6	3317	3.760	4.720	91	13.03	1.96	Quiet	
" 6	21.4	3337	3.590	4.540	92	12.43	1.86	"	Mch. 7. R Supra-renalectomy
" 9	23.2	3280	4.300	4.910	83	14.57	2.22	"	Suprarenal much enlarged
" 13	23.4	3309	3.400	4.600	98	12.00	1.81	"	
" 21	20.6	3285	3.720	4.890	96	12.96	1.97	"	
" 23	23.8	3288	3.320	4.360	96	11.55	1.76	"	
" 27	23.5	3345	3.520	4.540	94	12.23	1.83	"	
" 30	23.0	3262	3.990	4.440	81	13.43	2.06	"	
Apr. 1	22.2	3216	3.730	4.470	87	12.78	1.99	"	Mch. 28. L Supra-renalectomy
" 3	23.0	3187	3.560	4.660	95	12.45	1.95	"	
" 5	23.2	3217	3.930	4.900	91	13.53	2.10	"	
" 7	24.8	3216	3.880	4.580	86	13.22	2.06	"	
" 10	23.5	3223	3.310	3.980	87	11.38	1.77	"	
" 13	24.2	3202	3.880	4.580	86	13.22	2.06	"	
" 17	26.0	3253	3.930	4.440	82	13.30	2.04	"	
" 20	23.0	3159	3.760	4.490	87	12.84	2.03	"	
" 25	25.0	3210	3.870	4.440	83	13.17	2.05	"	
May 8	21.4	3162	3.670	4.580	91	12.65	2.00	"	

Protocol 2. Rabbit 284. Female — gray adult.

Sept. 13, 1921. Began metabolic studies.

Sept. 21. Under ether removed most of R and L thyroid lobes.

Oct. 1. Wound healed.

Oct. 27. Animal had been used for sheep cell antibody work.

Jan. 4, 1922. Under ether exposed thyroid area, searched for thyroid tissue, none found.

Jan. 10. Under ether removed R and L suprarenals completely. Abundant abdominal fat. No accessory suprarenal found.

Jan. 12. Somewhat dull, but eating ration.

Jan. 19. Wounds healed completely.

Jan. 21. Gave 25 mgm. KI by mouth.

Jan. 28. Hearty and strong.

Jan. 30. Gave 25 mgm. KI by mouth.

May 10. Being used for typhoid antibody work.

June 2. Nearly dead from intravenous injection of 1/4 cc. standard typhoid vaccine. Killed and autopsied at once. Thyroid lobes absent; there is a fragment of thyroid about 1 mm. in diameter at site of R stump ligature. Thymus atrophic, area replaced by fat; heart normal. Two small well encapsulated abscesses in lower right lobe of lung. Liver is small, flaccid and brownish yellow in color; distinct increase in lymphoid tissue in portal spaces. Kidneys very large brownish gray yellow, soft, high grade cloudy swelling. R and L suprarenals absent, sites clean. Ovaries are notably enlarged, bright yellow in color with many small graffian follicles. There is one large (0.5 cm. in length) and two small (1.0 mm. in diameter) accessory suprarenals near upper pole of R ovary and also two small (1 mm. in diameter) accessory suprarenals at upper pole of L ovary (all verified histologically). Abundant fat in all depositories. Spleen small; pancreas hyperemic; stomach mucosa normal. Rabbit had survived double suprarenalectomy indefinitely, probably due to abundant accessory cortical tissue.

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1921		grams							
Sept. 13	25.2	2760	3.550	4.455	91	12.30	2.23	Quiet	
" 15	24.0	2766	3.765	4.525	87	12.94	2.34	"	
" 19	21.2	2735	4.085	4.810	86	13.88	2.54	"	
" 27	22.0	2853	2.670	3.275	89	9.20	1.61	"	Sept. 21. Thyroid-ectomy
Oct. 3	24.3	2848	2.890	3.700	93	10.04	1.76	"	
" 7	24.4	2900	2.900	3.950	99	10.23	1.76	"	
Dec. 1	24.0	2945	2.420	3.110	93	8.44	1.43	"	
" 28	22.0	2880	2.420	3.380	102	8.68	1.51	"	
" 31	22.5	2927	2.980	3.670	90	10.22	1.75	"	
1922									
Jan. 3	20.0	2953	2.940	3.700	92	10.13	1.72	"	
" 6	21.5	2985	2.970	3.980	97	10.46	1.75	"	
" 12	21.5	2927	3.280	4.370	97	11.49	1.96	Dull	Jan. 4. Reoperated—no thyroid found Jan. 10. R and L Suprarenalectomy
" 14	21.5	2918	3.400	4.410	94	11.88	2.03	Quiet	
" 16	21.0	2872	3.260	4.300	96	11.40	1.98	Dull	
" 19	23.0	2922	3.080	4.140	98	10.80	1.85	"	
" 21	22.8	2905	3.130	4.060	94	10.93	1.88	"	
" 23	19.8	2840	3.450	4.020	85	11.70	2.06	"	
" 25	22.0	2851	2.950	3.910	96	10.36	1.82	"	Jan. 21. KI-25 mgm.
" 27	23.0	2846	3.190	3.990	91	11.02	1.94	Quiet	
" 30	22.0	2895	2.950	4.180	103	10.74	1.85	"	
Feb. 1	22.4	2895	2.860	3.930	100	10.10	1.74	"	
" 3	20.5	2916	3.320	4.330	95	11.57	1.98	"	
" 6	20.5	2977	3.130	4.390	102	11.28	1.89	"	
" 9	20.6	3006	2.850	4.020	103	10.33	1.72	"	
" 11	21.6	2987	3.140	4.150	96	11.00	1.84	"	
" 14	24.0	2929	2.910	4.130	103	10.61	1.81	"	
" 17	19.8	2940	3.280	4.150	92	11.36	1.93	"	
" 21	23.4	2953	2.910	3.860	96	10.23	1.73	"	
" 24	18.2	2951	3.060	4.120	98	10.75	1.82	"	
" 28	21.2	2944	3.280	4.230	94	11.39	1.93	"	
Mch. 3	20.5	2990	3.030	4.220	101	10.84	1.81	"	
" 7	22.5	3031	3.610	4.620	93	12.54	2.06	"	
" 17	17.8	2953	3.160	4.160	96	11.02	1.87	"	
" 21	20.6	2942	2.860	3.870	98	10.10	1.72	"	
" 28	24.0	2852	3.000	3.280	79	10.13	1.78	"	
Apr. 3	23.0	2770	2.870	3.160	80	9.65	1.74	"	
" 11	23.0	2777	3.050	3.230	77	10.17	1.83	"	
" 20	23.0	2765	2.780	3.770	99	9.76	1.77	"	
" 27	19.4	2814	3.200	4.190	95	11.19	1.99	"	

Protocol 3. Rabbit 287. Male — gray adult.

Sept. 13, 1921. Began metabolic studies.

Sept. 21. Under ether removed most of R and L thyroid lobes.

Dec. 27. Had been used for sheep cell antibody work.

Jan. 4, 1922. Under ether exposed thyroid area and searched for thyroid, none found.

Jan. 10. Under ether removed R and L suprarenals completely. Abundant abdominal fat. No accessory suprarenal seen.

Jan. 12. Active, eating.

Jan. 16. Respiration slow, fairly active, wounds healed.

Jan. 21. Gave 25 mgm. KI by mouth.

Jan. 28. Appears normal, active and hearty.

Jan. 30. Gave 25 mgm. KI by mouth.

Mch. 23. Head slightly rotated to left, chronic ear disease (external ears contain thick, reddish brown scales), active and hearty. Killed and autopsied at once. Well nourished, strong. A very vascular, actively hyperplastic mass of thyroid 3 mm. in diameter found on R side, none found on L. Thymus present, abundant lymphoid tissue accessory parathyroid in section; one small area of consolidation in each lower lobe of lungs. Heart appears normal; liver normal in gross appearance, microscopically, liver cells are very large with pale cytoplasm; spleen small; pancreas hyperemic. R and L suprarenals absent, sites clean; kidneys normal; stomach distended with food, mucosa normal; moderate fat in all depositories. Large hemorrhagic (3 mm. in diameter) accessory suprarenal in R spermatic cord, none found on L. Pituitary slightly enlarged. Pus in R middle ear, but brain and meninges appear normal.

TABLE III. *Rabbit 287.*

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	2 hours Total Calories.	Calories per kgrm. per hr.	Behavior of Animal	REMARKS
1921		grams							
Sept. 13	23.6	2830	3.355	4.210	91	11.62	2.05	Quiet	Sept. 21. Thyroid-ectomy
" 15	23.6	2731	3.685	4.330	85	12.61	2.31	"	
" 19	21.6	2701	4.045	4.445	80	13.58	2.51	"	
" 27	22.6	2808	3.305	3.940	87	11.27	2.01	"	
Oct. 3	22.7	2781	2.980	3.770	92	10.32	1.86	"	
" 7	25.0	2828	3.345	4.245	92	11.62	2.05	Rapid Resp.	Jan. 4. Reoperated—no thyroid found Jan. 10. R and L. Suprarenalectomy Resp. jerky and rapid
Dec. 28	22.0	2784	3.000	3.630	88	10.29	1.85		
" 31	22.5	2840	3.440	4.460	94	12.01	2.11	Quiet	
1922									
Jan. 3	23.5	2815	3.640	4.180	84	12.29	2.18	"	
" 6	21.5	2839	3.840	4.700	89	13.21	2.33	"	
" 12	20.0	2733	3.390	4.010	86	11.57	2.12	Dull	Jan. 21. KI—25 mgm.
" 14	21.5	2752	3.500	4.320	90	12.03	2.19	Quiet	
" 16	21.0	2672	3.390	3.450	74	11.22	2.10	Dull	
" 19	23.0	2602	3.450	3.800	80	11.61	2.23	Quiet	
" 21	22.8	2593	3.050	3.600	86	10.39	2.00	"	
" 23	19.8	2635	3.190	3.960	90	11.03	2.09	Quiet-dull	Ataxic
" 25	22.0	2626	3.450	4.270	90	11.89	2.26	Quiet	
" 27	23.0	2585	3.170	3.840	88	10.89	2.11	Slight dyspnoea	
" 30	22.2	2585	3.200	4.190	95	11.19	2.16	Quiet	
Feb. 1	22.4	2629	2.920	3.930	98	10.25	1.95	"	
" 3	20.5	2647	3.300	4.220	93	11.46	2.16	"	Ataxic
" 6	20.5	2637	3.440	4.000	85	11.65	2.21	"	
" 9	20.6	2646	3.360	4.000	87	11.44	2.16	"	
" 11	21.6	2612	3.700	4.240	83	12.58	2.41	"	
" 14	24.0	2613	3.630	4.040	81	12.22	2.34	"	
" 17	19.8	2600	3.320	3.790	83	11.24	2.16	"	Ataxic
" 21	23.4	2630	2.930	3.650	91	10.08	1.92	"	
" 24	18.2	2661	3.480	4.140	87	11.84	2.22	"	
" 28	21.2	2674	3.400	4.050	87	11.58	2.17	"	
Mch. 3	20.5	2650	3.510	3.810	79	11.76	2.22	"	
" 7	22.5	2663	3.030	3.820	92	10.46	1.96	"	Ataxic
" 13	23.6	2634	2.810	3.280	85	9.55	1.81	"	
" 17	17.8	2659	3.110	3.770	88	10.69	2.01	"	
" 21	20.6	2617	3.210	3.680	83	10.92	2.05	"	

Protocol 4. Rabbit 288. Male — gray adult.

Sept. 4, 1921. Began metabolic studies.

Nov. 15. Under ether removed most of R and L thyroid lobes.

Jan. 10, 1922. Under ether removed R and L suprarenals completely. No accessory suprarenals seen; moderate abdominal fat; kidneys appear normal.

Jan. 12. Eating ration.

Jan. 17. Wounds healed. Active.

Jan. 21. Gave 25 mgm. KI by mouth.

Jan. 30. Gave 25 mgm. KI by mouth.

Mch. 17. Weight 1948 gm. Started glycerol extract of fresh ox suprarenal cortex, 5 cc. daily.

Mch. 30. Weight 2074 gm.

Apr. 15. Snuffles.

Apr. 24. Stopped suprarenal cortex.

Apr. 27. Not eating. Marked snuffles.

Apr. 28. Died. Weight 1880. gm. Autopsy while still warm. Two small, vascular thyroid masses about 1 mm. in diameter on R side, histologically both were actively hyperplastic; none on L. Thymus present, abundant lymphoid tissue; lungs normal; heart dilated and flabby. R and L suprarenals absent, sites clean; no accessory suprarenals found. Liver very dark red, small well marked increase in lymphoid tissue in portal spaces; pancreas hyperemic; spleen small; kidneys moderately pitted; testes smaller than normal; stomach contains considerable fluid, no food, mucosa intact. Aorta sclerotic at arch and at bifurcation.

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1921									
Sept. 20	23.5	2140	3.905	4.670	87	13.36	3.12	Restless	
" 28	24.7	2141	3.685	4.585	90	12.77	2.98	"	
Nov. 4	22.0	2216	2.890	3.260	82	9.34	2.11	Quiet	
" 11	23.0	2172	2.850	3.110	79	9.60	2.21	"	
" 22	21.0	2344	2.790	3.570	93	9.69	2.07	"	Nov. 15. Thyroid-ectomy
" 30	22.0	2451	3.090	3.750	88	10.63	2.17	"	
Dec. 7	22.0	2511	2.950	4.030	99	10.43	2.08	"	
1922									
Jan. 5	22.0	2584	2.960	3.880	95	10.36	2.01	"	Snuffles
" 9	22.0	2557	3.020	3.920	94	10.56	2.06	"	Jan. 10. R and L
" 12	20.0	2420	2.870	3.290	83	9.76	2.02	"	Suprenalectomy
" 14	21.5	2405	2.880	3.550	90	9.89	2.06	"	
" 16	21.0	2393	2.950	3.740	92	10.24	2.14	"	
" 19	23.0	2336	2.860	3.470	88	9.84	2.11	"	
" 21	22.8	2316	2.820	3.360	87	9.61	2.07	"	
" 23	19.8	2394	3.000	3.590	87	10.27	2.14	"	Jan. 21. KI—25 mgm.
" 25	22.0	2435	3.070	4.030	95	10.76	2.21	"	
" 27	23.0	2334	2.530	3.530	101	9.07	1.94	"	
" 30	22.0	2298	2.810	3.580	93	9.72	2.11	"	
Feb. 1	22.4	2243	2.380	3.160	97	8.31	1.85	"	
" 3	20.5	2210	2.490	2.950	86	8.51	1.93	"	Jan. 30. KI—25 mgm.
" 6	20.5	2278	2.930	3.700	92	10.13	2.22	"	
" 9	20.6	2302	3.070	4.050	96	10.73	2.33	"	
" 11	21.6	2286	2.970	3.860	95	10.31	2.26	"	
" 14	24.0	2235	2.760	3.500	92	9.58	2.14	"	
" 17	19.8	2169	3.000	3.480	84	10.23	2.36	"	
" 21	23.4	2160	2.200	3.190	105	8.20	1.90	"	
" 24	18.2	2168	2.720	3.390	91	9.36	2.16	"	
" 28	21.2	2112	2.890	3.360	85	9.78	2.32	"	
" 3	20.5	2105	2.500	3.040	88	8.62	2.05	"	
Mch. 7	22.5	2043	2.330	2.770	86	7.99	1.96	"	
" 13	23.4	2017	2.830	2.950	82	8.84	2.19	"	
" 17	17.8	1992	2.270	3.000	96	7.95	2.00	Quiet-dull	
" 20	20.6	1978	2.820	3.340	86	9.64	2.44	Quiet	
" 28	24.0	2077	2.890	3.490	86	11.54	2.38	"	Mch. 17. Adr. cortex emulsion (5cc. daily)
Apr. 3	23.0	2062	2.750	3.270	86	9.44	2.29	"	
" 7	24.8	2059	2.880	3.260	82	9.77	2.37	"	
" 11	25.0	1998	2.750	3.000	79	9.26	2.32	"	
" 17	25.5	2048	2.750	3.050	81	9.23	2.25	"	
" 20	23.0	2057	2.940	3.260	81	9.86	2.40	"	
" 24	24.0	2115	3.050	3.380	81	10.22	2.42	"	

Protocol 5. Rabbit 291. Male — adult, black.

Sept. 21, 1921. Began metabolic studies; used for antibody work.

Jan. 18, 1922. Under ether removed spleen.

Feb. 2. Under ether removed most of R and L thyroid lobes.

Mch. 7. Under ether removed R suprarenal.

Mch. 28. Under ether removed L suprarenal; moderate abdominal fat, slight pitting of kidney cortex.

Apr. 1. Active, eating well.

Apr. 9. Soft stools, dull, not eating well.

Apr. 14. Soft stools, losing weight, eats carrot, but very little oats.

Apr. 18. Weaker, eats very little carrot. Snuffles.

Apr. 22. Died this morning, autopsy at once. R and L thyroid lobes absent, no accessories found. On microscopic examination of thyroid area a few hyperplastic follicles found attached to thyroid cartilage. Thymus atrophic; lungs normal; heart small and contracted; liver small, flaccid, very dark brown; spleen absent, no accessories found. R and L suprarenals absent. One small 1 mm. hemorrhagic accessory found in L spermatic cord, no others found after careful search. Kidneys show slight pitting of cortex. Moderate abdominal fat. Testes normal; stomach contains moderate amount of food and fluid, mucosa intact. Hypophysis not notably enlarged. Microscopic examination — slight lymphoid infiltration in portal spaces of liver and in kidney.



TABLE V.  
*Rabbit 291.*

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1921		grams							
Sept. 21	23.5	2212	4.065	4.695	84	14.55	3.29	Restless	Jan. 18. Splenectomy.
" 28	24.2	2272	4.165	5.185	91	14.32	3.15	"	
Nov. 5	20.5	2497	3.350	4.720	102	12.13	2.43	Quiet	Feb. 2. Thyroidectomy
" 11	23.0	2402	3.300	3.730	82	11.18	2.33	"	
Dec. 7	22.4	2515	3.610	4.490	90	12.50	2.49	"	
1922									
Jan. 5	22.0	2537	3.620	4.540	91	12.53	2.47	"	Mch. 7. R Supra-renalectomy.
" 20	21.5	2380	3.870	4.670	88	13.24	2.78	"	
" 23	19.8	2475	3.930	5.160	95	13.78	2.78	Restless	
" 25	22.0	2459	3.610	4.620	93	12.54	2.55	Quiet	Mch. 28. L Supra-renalectomy.
" 27	23.6	2441	3.380	4.020	86	11.60	2.38	"	
" 30	23.5	2508	3.710	4.660	91	12.87	2.57	"	
Feb. 1	23.0	2515	3.840	4.960	94	13.36	2.66	"	
" 9	22.0	2637	3.170	4.260	98	11.11	2.11	"	
" 16	19.0	2611	2.930	4.040	100	10.38	1.99	"	
" 23	24.0	2736	3.060	3.970	94	10.69	1.95	"	
" 28	21.4	2730	2.540	3.880	111	9.97	1.83	"	
Mch. 7	22.5	2790	2.940	3.930	97	10.33	1.85	"	
" 10	23.2	2753	2.280	3.550	113	9.12	1.66	"	
" 13	23.4	2747	2.930	3.820	95	10.20	1.86	"	
" 20	23.2	2799	2.620	3.710	103	9.53	1.70	"	
" 27	23.0	2850	2.700	3.830	103	9.84	1.73	"	
" 30	23.0	2770	2.790	3.270	85	9.52	1.72	"	
Apr. 1	21.8	2764	3.210	3.990	90	11.11	2.01	"	
" 3	23.0	2774	2.900	3.770	95	10.07	1.82	"	
" 5	23.2	2732	2.600	3.310	93	8.99	1.64	"	
" 7	22.5	2692	3.030	3.540	85	10.31	1.91	"	
" 10	23.5	2740	2.530	3.100	89	8.71	1.59	"	Diarrhea: urinous odor
" 13	23.8	2620	2.220	2.800	92	7.67	1.46	"	Mkd. asthenia
" 17	24.2	2692	2.170	2.450	82	7.34	1.36	"	
" 20	23.0	2459	1.840	2.160	85	6.29	1.28	Moribund	

Protocol 6. Rabbit 306. Female — black and white. (Born in Laboratory, July 1, 1921.)

Dec. 2, 1921. Began metabolic studies.

Jan. 18, 1922. Under ether removed spleen.

Feb. 2. Under ether removed most of R and L thyroid lobes.

Mch. 7. Under ether removed R suprarenal.

Mch. 28. Under ether removed L suprarenal.

Apr. 1. Slight purulent discharge from nose.

Apr. 10. Chronic bilateral external ear disease.

Apr. 29. Eating well, but dull.

May 31. Under ether froze R and L ovaries with ethyl chloride. Ovaries notably enlarged and bright yellow in color.

June 5. Has shown no effects of freezing ovaries, active and strong, in excellent condition. Killed. Both ears contain large masses of thick, dry, brownish scales, putrefactive odor. Skin of body is dry and scaly and fur thin. No thyroid found on careful search, area saved for microscopic examination. Thymus atrophic, area replaced by fat. Each lung shows a very small area of consolidation along anterior margin of upper lobes. Heart normal; liver seems very small, otherwise normal; spleen absent, no accessories found; pancreas not hyperemic. R and L suprarenals absent, sites clean. In the capsule of L kidney near upper pole is a large accessory suprarenal 2 x 3 mm. with large veins emerging and draining into L lumbo-suprarenal vein. Two small (1 mm. in diameter) accessories at upper pole of R ovary, each with a separate large vein draining into L ovarian vein. Kidneys smooth, normal; abundant abdominal fat. Pituitary perhaps slightly enlarged.

TABLE VI. *Rabbit 306.*

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per km. per hour	Behavior of Animal	REMARKS
1921		grams							
Dec. 2	24.5	1833	2.860	3.150	80	9.62	2.63	Quiet	
" 7	21.8	1847	2.770	3.310	87	9.47	2.56	"	
1922									
Jan. 5	21.8	1949	3.390	3.430	74	11.15	2.86	Restless	Ears scalded, sloughing
" 12	21.0	1992	3.220	4.220	95	11.27	2.83	"	Ears healed
" 17	24.0	1954	3.060	3.510	83	10.41	2.66	Quiet	Jan. 18. Splenectomy
" 20	21.5	1916	3.150	3.940	91	10.88	2.84	"	Moisture
" 23	20.2	2000	3.420	4.360	93	11.84	2.96	"	"
" 25	22.0	1954	3.350	3.880	84	11.40	2.92	"	"
" 27	23.6	1938	3.110	3.690	86	10.65	2.75	"	"
" 30	25.5	1880	3.140	3.560	82	10.67	2.84	"	"
Feb. 1	22.4	1886	2.910	3.510	88	9.95	2.65	"	"
" 10	26.6	2008	2.480	3.030	89	8.51	2.12	"	Feb. 2. Thyroidectomy
" 21	24.6	2157	2.540	3.160	90	8.80	2.04	"	"
" 27	22.8	2223	2.520	3.300	95	8.81	1.98	"	"
Mch. 6	21.4	2204	2.650	3.460	95	9.24	2.10	"	"
" 9	22.8	2278	2.550	3.450	98	9.00	1.98	"	"
" 11	20.2	2203	2.620	3.450	96	9.14	2.08	"	Mch. 7. R Supra-renalectomy
" 14	22.2	2264	2.520	3.400	98	8.87	1.96	"	"
" 17	19.8	2207	2.960	3.630	89	10.20	2.31	"	"
" 20	23.2	2211	2.420	3.160	95	8.44	1.91	"	"
" 23	23.2	2170	2.960	3.460	85	10.07	2.32	"	"
" 27	23.0	2285	2.150	3.150	107	8.09	1.77	"	"
" 30	23.0	2201	2.850	3.320	85	9.67	2.20	"	Mch. 28. L Supra-renalectomy
Apr. 1	21.8	2231	2.720	3.320	89	9.33	2.09	"	"
" 3	23.0	2238	2.770	3.620	95	9.67	2.16	"	"
" 5	23.2	2257	3.040	3.680	88	10.43	2.31	"	"
" 7	24.8	2264	2.640	3.560	98	9.29	2.05	"	"
" 10	22.5	2290	2.360	3.240	100	8.32	1.82	"	Bilateral ear infection
" 13	23.8	2238	2.480	3.280	96	8.69	1.94	"	"
" 17	25.5	2278	2.680	3.270	89	9.19	2.02	"	"
" 20	22.5	2160	2.410	3.280	99	8.49	1.97	"	External and middle ear infection
" 25	25.0	2207	2.770	3.250	85	9.46	2.14	"	Odor of putrefaction
May 8	21.6	2206	2.710	3.280	87	9.32	2.11	"	"

Protocol 7. Rabbit 323. Male — white adult.

Jan. 18, 1922. Began metabolic studies.

Feb. 2. Under ether removed most of R and L thyroid lobes, enlarged and hyperemic.

Feb. 28. Under ether removed R suprarenal. Rabbit has always been dull and inactive.

Apr. 11. Under ether removed L suprarenal; kidneys normal; abundant fat.

Apr. 14. Eating well, as active as usual.

Apr. 20. Wounds healed, stiches removed.

July. 7. Has been used in antibody studies. Apparently normal. Killed. Weight 2233 gm. One large thyroid fragment 3 x 2 mm. on R side at site of ligature. None found on L. External paras normal; thymus atrophic; heart and lungs normal; liver normal; kidneys normal. R and L suprarenals absent, sites clean, no accessory suprarenals found in region of suprarenals nor along path of descent of testes. Testes examined carefully for accessories. Two and probably three small ones found. Testes smaller than usual. Spleen small; pancreas hyperemic; abundant abdominal fat; lymph glands not enlarged.

TABLE VII. *Rabbit 323*

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1922		grams							
Jan. 26	21.6	2354	3.320	4.480	98	11.69	2.48	Quiet	Two runs for training
" 28	22.0	2374	3.370	4.480	97	11.78	2.48	"	
Feb. 1	24.0	2455	3.520	4.240	88	12.02	2.45	"	
" 10	23.0	2365	2.950	4.160	103	10.69	2.26	"	Feb. 2. Thyroid-ectomy
" 17	20.0	2357	2.670	3.250	89	9.13	1.94	"	
" 24	20.6	2442	2.600	3.480	97	9.15	1.87	"	
Mch. 3	22.0	2459	2.400	3.240	98	8.45	1.72	"	
" 17	19.6	2493	2.770	3.550	93	9.64	1.93	"	Cyanotic
" 23	21.8	2506	2.890	3.590	90	10.00	1.99	"	
" 27	23.5	2585	2.710	3.600	97	9.46	1.83	"	
" 30	22.0	2446	3.010	3.710	90	10.33	2.11	"	Mch. 28. R Supra-renalectomy
Apr. 6	22.5	2447	2.870	3.690	94	9.94	2.03	"	
" 13	23.2	2522	2.860	3.670	93	9.96	1.98	Dull	
" 15	23.2	2550	2.830	3.880	100	9.97	1.95	"	Apr. 11. L Supra-renalectomy
" 17	26.0	2470	2.810	3.420	89	9.61	1.95	"	Marked asthenia
" 20	22.5	2448	2.760	3.700	97	9.73	1.99	"	
" 22	23.8	2322	2.630	3.420	95	9.13	1.97	"	
" 24	21.8	2453	3.090	3.810	90	10.61	2.16	Quiet	Unable to hold head up
" 27	17.6	2370	3.070	4.080	97	10.73	2.26	"	Ear disease
May 1	25.2	2380	2.730	2.930	78	9.13	1.92	Very dull	
" 8	21.4	2347	2.880	3.330	84	9.79	2.08		Severe ear disease
" 16	21.2	2360	3.040	3.800	91	10.49	2.22	Dull	No asthenia

Protocol 8. Rabbit 325. Female — gray adult.

Jan. 25, 1922. Began metabolic studies.

Mch. 7. Under ether removed most of R and L thyroid lobes, vascular, slightly enlarged.

Apr. 5. Under ether removed R suprarenal, enlarged.

Apr. 11. Under ether removed L suprarenal and one small accessory on peritoneum slightly external to gland.

Apr. 14. In good condition, eats well.

Apr. 18. No evidence of suprarenal injury has developed, active, hearty and strong.

July 10. Was bred several times since Apr. 18, but never became pregnant. Killed, autopsy at once. There is a fragment of very hyperemic thyroid 3 x 1 mm. on L side and on R side there are two small fragments (1) 2 x 1 mm. and (2) 1 x 1 mm. The two external parathyroids are normal in size and appearance. Thymus atrophic, area replaced by fat; lungs and heart normal; liver is very large, surface lobulated, many minute white fibromata in capsule. The lower liver is unusually large, about twice the weight of the upper. R suprarenal absent. At site of L suprarenal there is a thin mass 2 x 2 mm. of bright yellow tissue surrounding old ligature. Microscopic examination shows only pigmented fat. At upper pole of R ovary there is a very vascular large accessory adrenal 5 x 2.5 mm. Ovaries are very large, two or three times normal size, bright yellow in color with many small graafian follicles. Kidneys are normal; spleen small; pancreas not hyperemic; stomach distended with food, mucosa intact.

TABLE VIII. *Rabbit 325.*

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1922		grams							
Jan. 28	22.2	2333	3.180	4.340	99	11.24	2.41	Quiet	Two runs for training
Feb. 2	23.2	2395	3.570	4.340	88	12.30	2.56	Rapid Resp.	
" 4	20.6	2389	3.460	4.240	89	11.91	2.49	Quiet	
" 7	20.5	2391	3.420	4.030	86	11.63	2.43	"	
" 10	24.0	2403	3.410	4.340	93	11.78	2.45	"	Mch. 7. Thyroid-ectomy
" 21	24.4	2442	3.420	4.210	90	11.72	2.40	"	
Mch. 4	22.0	2603	3.920	4.970	92	13.61	2.61	"	
" 14	21.2	2720	3.090	4.080	96	10.81	1.99	"	
" 21	21.0	2698	3.040	3.970	95	10.60	1.97	"	Apr. 5. R Supra-renalectomy Apr. 11. L Supra-renalectomy Recently pregnant
" 28	20.5	2770	2.770	3.890	102	9.99	1.80	"	
Apr. 13	23.2	2790	2.930	3.840	95	10.26	1.87	"	
" 15	23.5	2791	2.880	4.000	101	10.27	1.84	"	
" 17	26.0	2746	3.660	3.980	79	12.28	2.24	"	
" 20	22.5	2714	3.570	4.020	82	12.04	2.22	"	
" 22	23.8	2672	3.140	4.030	93	10.94	2.05	"	
" 24	21.8	2715	3.760	4.560	88	12.93	2.38	"	
" 27	17.6	2672	3.440	4.260	90	11.86	2.22	"	
May 1	25.2	2728	3.280	3.810	85	11.09	2.03	"	
" 8	21.0	2696	3.310	3.940	87	11.27	2.09	"	
" 13	23.2	2682	3.120	3.860	90	10.75	2.00	"	
" 16	21.2	2712	3.290	4.320	95	11.54	2.13	"	

Protocol 9. Rabbit 326. Fawn colored female.

Jan. 25, 1922. Began metabolic studies.

Mch. 7. Under ether removed most of R and L thyroid lobes, enlarged and hyperemic.

Apr. 5. Under ether removed R suprarenal.

Apr. 11. Under ether removed L suprarenal.

Apr. 14. Active, hearty; has shown no dullness since operation.

Apr. 18. In heat, bred.

May 19. Gave birth to 6 young.

July 8. Reared and weaned young. Under ether removed R and L ovaries, distinctly enlarged and bright yellow. Examination of ovarian region for accessory suprarenals unsatisfactory.

July 12. Weight 2249 gm. In excellent condition, no reaction from gonadectomy. Killed. Breasts involuting rapidly. Two accessory (?) thyroids in midline, one on fascia at notch on upper border of thyroid cartilage about 1 mm. in diameter and another a few mm. above, about 0.5 mm. in diameter. (It is possible these may be auto transplants from fragments dropped at time of removal). There is another thin veil of thyroid tissue on anterior surface of trachea in region of old isthmus. No thyroid found on L side. On R side there are two separate fragments each about 1 mm. in size, hyperemic. External parathyroids normal; thymus atrophic, no fat in area; lungs and heart normal; liver normal; spleen slightly enlarged; pancreas hyperemic. R and L suprarenals absent. Large accessory suprarenal 3 x 1.5 mm. on lateral abdominal wall, external and above kidney. A large, long vein extends directly into the renal vein. No definite suprarenal tissue in region of ovaries. R and L ovaries absent. Sites examined histologically. On R side below renal artery is a grayish yellow mass 4 x 1 mm. possibly suprarenal or lymph gland. Kidneys normal; stomach distended with food, mucosa normal. Very little fat visible anywhere.



TABLE IX. *Rabbit 326*

DATE	Room Temperature	Weight of Rabbit	O <sub>2</sub> in grams, 2 hours	CO <sub>2</sub> in grams, 2 hours	R. Q.	Total Calories, 2 hours	Calories per kgm. per hour	Behavior of Animal	REMARKS
1922		grams							
Jan. 28	22.2	2549	3.580	4.410	90	12.28	2.41	Quiet	Two runs for training
Feb. 2	23.8	2650	3.860	4.880	92	13.36	2.52	"	
" 4	20.6	2702	3.760	4.600	89	12.93	2.39	"	
" 7	20.5	2708	4.240	5.070	87	14.50	2.68	"	
" 21	24.4	2600	3.480	4.360	91	12.04	2.31	"	Mch. 7. Thyroid-ectomy
Mch. 14	21.2	2902	3.150	4.460	103	11.46	1.97	"	
" 21	21.0	2922	3.390	4.140	95	11.78	2.02	"	Apr. 5. R Supra-renalectomy
" 27	23.5	2997	2.910	4.050	101	10.40	1.74	"	Apr. 11. L Supra-renalectomy
" 28	24.0	2983	3.700	4.040	79	12.47	2.09	"	Bred Apr. 18
Apr 13	23.2	3002	3.610	4.850	98	12.65	2.11	"	
" 15	23.5	2989	3.170	4.390	101	11.28	1.89	"	
" 20	26.0	2916	2.990	3.750	91	10.35	1.78	"	
" 20	22.5	2932	3.590	4.710	95	12.58	2.10	"	
" 22	23.8	2921	3.160	4.000	92	10.95	1.87	"	
" 24	21.8	2972	3.280	4.320	100	11.61	1.95	"	
" 27	17.6	3022	3.760	5.020	97	13.20	2.18	"	
May 1	25.2	3170	3.660	4.210	84	12.37	1.95	"	
" 8	21.0	3281	4.140	5.270	93	14.31	2.18	"	
" 13	23.2	3310	4.200	4.950	86	14.29	2.16	"	
" 16	21.2	3383	4.680	5.570	87	15.93	2.35	"	Near term—placed in large cage.
" 18	20.8	3366	5.100	5.570	79	17.19	2.60	"	May 20. Gave birth
" 26	25.0	2922	3.640	4.770	95	12.74	2.18	"	to young
June 17	23.0	2427	3.640	4.940	99	11.79	2.43	Quiet	Nursing young
" 26	23.6	2287	4.030	3.240	90	11.22	2.45	"	"
" 28	25.2	2272	3.400	2.970	83	10.09	2.22	"	"

The more important general data of the nine experiments here reported and also of the six experiments previously reported are summarized in Table X.

TABLE X.

Sex	Rabbit No.	Interval before Thyroidectomy	Interval between Thyroidectomy and removal of 2nd Suprarenal	Duration of life after double Suprarenalectomy	Average normal metabolism Calories per kg. per hr.	Average metabolism after Thyroidectomy Calories per kg. per hr.	Percentile decrease after Thyroidectomy	Average metabolism during first two weeks following Suprarenalectomy Calories per kg. per hr.	Percentile increase or decrease after Suprarenalectomy	Fragments or Accessory Thyroids at Autopsy	Accessory Suprarenals at Autopsy *	REMARKS
		da.	da.	da.								
m	271	14	23	20 Died	2.25	1.86	17	1.62	-13	none found	none found	
m	267	14	23	35 Died	2.33	1.92	18	1.68	-12	none found	none found	
m	270	14	23	26 Died	2.41	2.04	15	1.87	-8	1-2 mm. fragment	none found	
m	272	14	23	Indef. 63	2.62	1.95	26	1.82	-7	2 fragments 1x2 mm.	7 large	
m	291	134	54	Killed 25	2.54	1.84	28	1.75	-5	few follicles microscopical trace	1-1 mm.	Splenectomy
f	266	14	23	14 Died	2.67	1.83	31	1.83	0	microscopical 2-1 mm. fragments	none found none found	KI
f	306	62	54	Indef. 69	2.62	2.05	22	2.08	0	none found	2-1 mm. 1-3x2 mm.	Splenectomy KI
f	326	38	35	Killed Indef. 94	2.50	1.95	22	1.98	0	2 accessories 3 fragments 1 mm.	1-3x1.5 mm. 1-0.5 mm. possibly others	
m	323	7	54	Killed Indef. 87	2.47	1.93	22	2.00	+4	1-3x2 mm. fragment	3-1 mm.	
m	287	8	111	Killed Indef. 72	2.29	2.01	10	2.12	+5	1-3 mm. fragment	1-3 mm.	KI
m	269	14	23	Killed Indef. 63	2.25	1.77	21	1.87	+6	1-2 mm. fragment	7	
f	283	140	56	Killed Indef. 109	2.28	1.89	17	2.00	+6	1-3x3 fragment	2 large	Splenectomy
f	325	41	35	Killed Indef. 91	2.48	1.92	23	2.12	+10	1-3x1 2-2x1 fragments	1-5x3 mm. 1-2 mm.	
f	284	8	111	Killed Indef. 143	2.37	1.72	27	1.94	+13	1-1 mm. fragment	5 1 very large	KI

\* Complete surgical removal of both main glands had been made in all cases as shown by careful gross and microscopic autopsy checks.

Very carefully search was made for fragments of or accessory suprarenal tissue and also for thyroid tissue at autopsy. All definite or suggestive masses were checked by histological examination. In every case both main suprarenal glands were found to have been completely removed. In ten of the fifteen cases accessory suprarenal cortical tissue was demonstrated. As many as seven separate accessory masses have been found in a single animal. These masses in the rabbit are most frequently found along the spermatic vessels and on the epididymis or in the region of the upper pole of the ovary and less rarely in the neighborhood of the main suprarenal glands. On account of hypertrophy they are, of course, more readily detected if the animal survives double suprarenalectomy for a month or more. In five of the fifteen cases we were unable to demonstrate accessory suprarenal tissue. These five animals died of suprarenal insufficiency on the 14th, 20th, 26th, 35th, and 118th day after removal of the second suprarenal. The rabbit (288) that survived 118 days lost approximately 600 gm. in weight in 66 days. At this time a glycerol emulsion of fresh ox suprarenal cortex was added to the diet. This improved his clinical condition and possibly prolonged his life. Another rabbit died on the 25th day. In this animal one 1 mm. accessory suprarenal was found. The remaining nine rabbits survived double suprarenalectomy indefinitely in excellent condition and in all of these either very large or multiple accessory suprarenal glands were found. If further data were needed this is striking evidence of the relation of survival to the presence or absence of accessory cortical tissue.

It is as difficult to perform a complete thyroidectomy in rabbits as it is easy to perform complete removal of the main suprarenal glands. Occasionally one finds a rabbit with the thyroid lobes located rather low so that they are easily detached from the lower border of the thyroid cartilage. When the thyroid lobes are firmly attached to the thyroid cartilage invisible or undetected fragments are often left behind or even a few cells may be broken off in handling the lobes which act as autotransplants. As thyroid tissue is very resistant, easily transplantable, and capable of rapid regeneration a large percentage of rabbits will show gross regenerating thyroid masses if examined a month or more after thyroidectomy.

In twelve of the fifteen rabbits we were able to demonstrate thyroid tissue after death. In two of these only a few thyroid follicles were found by examining serial microscopic sections of the thyroid area. These data concerning accessory and unremoved portions of the suprarenal and thyroid glands are mentioned merely to emphasize one of the difficulties encountered in interpreting experiments involving extirpation not only of these two glands but of any of the so called ductless glands.

The respiratory exchange measurements were made with the modified Haldane open circuit apparatus under constant conditions as regards diet and time of feeding. Objective records of movement were not made. Rabbits for the most part after a period of training remain quiet, otherwise, they have been discarded. We believe that preliminary periods of training and observation are essential. Movement in animals cannot be completely controlled or evaluated. After a great deal of experience we have come to the conclusion that the best safeguards in evaluating the movement factor in heat production measurements in experiments of this nature in animals is obtained by increasing the number of individual observations and by using a two hour observation period. The tables of heat production accompanying the protocols give all of the measurements taken on a given animal and indicate sufficiently well that with these precautions movement as a cause for errors in interpretation may be neglected.

In Table X the number of days during which control or normal heat production measurements for each animal were obtained, is given; also the number of days between thyroidectomy and the removal of the second suprarenal gland and finally the number of days under observation after double suprarenalectomy. The normal metabolic rates show the usual variations for different animals. The decrease in heat production following thyroidectomy also shows great variations, the greatest drop being 31 per cent., the least 10 per cent. and the average 21 per cent. These differences are due to many factors, one of which is clearly the functional capacity and physiological value of the unremoved thyroid tissue. Next, the experiments have been arranged in this table to show the changes in heat production during the first two weeks following suprarenalectomy. In two of these experiments there

was a drop in heat production of more than 10 per cent. below the average level after thyroidectomy alone and in two or 13 per cent. there was a significant rise above the level obtaining after thyroidectomy. In one it was 10 per cent. and in the other 13 per cent. Rises of from 4—6 per cent. were obtained in four others after suprarenalectomy, and while we think they have the same significance as the two in which the rises were higher, they may be considered as possibly within the limits of experimental error. While the rise or fall in metabolism after suprarenalectomy cannot be brought into an exact, graduated relation with the presence or absence of thyroid or suprarenal tissue as determined postmortem, there is a definite general relationship in that those with decreased metabolism after suprarenalectomy showed the least thyroid and suprarenal tissue postmortem, and those with increased metabolism after suprarenalectomy showed the most thyroid and suprarenal tissue. The essential and striking feature of these experiments is the *absence* of a significant rise in heat production in thirteen of the fifteen experiments. In the other two, relatively large amounts of accessory cortical tissue and unremoved fragments of thyroid were found. In suprarenal-ectomized rabbits with intact thyroids a rise of over 10 per cent was obtained in twenty-eight out of thirty-eight experiments or 74 per cent. These data, it seems to us, clearly establish the facts that the presence of the thyroid gland is a factor in bringing about the rise in heat production following partial suprarenalectomy, and the absence of the thyroid is likewise a factor in the failure to obtain a rise after partial suprarenal-ectomy. As pointed out in previous papers, the necessary increase in the discharge of the iodine-containing hormone from the thyroid required to produce the increased respiratory exchange after suprarenal removal, could hardly be explained through stimulation by epinephrin. It therefore appears rather to be in some way dependent upon a weakness of the cortex function. In the operation of double suprarenalectomy most of the epinephrin secreting tissue is, of course, removed, and yet in spite of this loss an increase in thyroid activity occurs in the majority of cases. This suggests that while epinephrin may stimulate the thyroid directly, the withdrawal of cortical control is a much more powerful activator of thyroid activity and the consequent discharge of thyroxin. If, therefore, epin-

ephrin stimulation could be combined with decreased cortical control, a very much more marked increase in thyroid activity and heat production could, in our opinion, be brought about. This would probably simulate what occurs during the Goetsch test and to some extent the conditions usually present in Graves' disease. Aub, Bright and Uridil<sup>5</sup> have observed that in cats thyroxin causes an increase in heat production, after suprarenalectomy as well as before this operation. We have observed similar reactions to desiccated thyroid in rabbits after suprarenalectomy alone and after thyroidectomy plus suprarenalectomy. We also have some data indicating that suprarenalectomized rabbits may be more sensitive to desiccated thyroid, just as to many other drugs, than are "normal" rabbits. The reaction of the animal with increased heat production is, of course, the same whether the iodine containing hormone is artificially introduced or caused to be discharged from the animal's store in the thyroid gland by the withdrawal of a regulatory or inhibitory influence of the suprarenal cortex. As evidence, however, for or against a thyroid-suprarenal interrelation such observations are irrelevant.

Three of the rabbits (284, 287 and 288) were given 50 mgm. KI, by mouth, in doses of 25 gm. on the eleventh and twentieth days after suprarenalectomy. In two, very distinct and prolonged though small rises, followed by falls in the respiratory exchange were noted. The third rabbit, while not showing the curve noted in the first two, maintained an indefinite rise. This rabbit also happened to show the largest post-suprarenal-ectomy rise in heat production and was the only one showing a rise of more than 10 per cent. Postmortem examination showed considerable unremoved thyroid tissue. Subsequent observations have shown that the failure to obtain a rise in heat production in many of our earlier experiments on rabbits and cats was probably due to exhaustion of the iodine store in the thyroid. Scott<sup>3</sup> noted a rise in heat production following the administration of iodine to cats with their suprarenals crippled by ligation or by freezing. In this connection, mention should be made of the fact that suprarenal injury appears to cause a rapid depletion of the iodine store of the thyroid both in rabbits and in cats. The details of these experiments will appear in another paper. Black, Hupper and Rogers<sup>6</sup> have

reported that feeding an "adrenal residue" to dogs caused an increase in the iodine store of the thyroid.

#### CONCLUSIONS.

Thyroidectomy abolishes or greatly lessens the rise in heat production which normally follows sufficient injury of the suprarenal function in rabbits.

These nine experiments furnish additional evidence that a thyroid-suprarenal cortex interrelationship exists, which is separate from the thyroid chromophil tissue interrelationship. The nature of this relationship is unknown but the evidence suggests that the suprarenal cortex, as one of its functions, exercises an inhibitory or regulatory control over thyroid activity and when this is sufficiently crippled, as by vessel ligation, freezing, or partial removal, the thyroid automatically responds with increased functional activity, resulting in increased heat production if a sufficient amount of the iodine containing hormone is liberated. There is evidence that single doses of iodine (25 mgms. KI), administered by mouth, increase the heat production in suprarenalectomized rabbits with incomplete thyroidectomies. There is also evidence that sufficient but sub-lethal suprarenal insufficiency in rabbits and in cats causes a rapid loss of iodine from the thyroid.

These observations throw light on the thyroid-sex gland interrelationship known since antiquity and probably have an important bearing both on the etiology of simple goiter and of exophthalmic goiter.

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NOTE: The respiratory exchange measurements were made by Miss Anna Cipra and Miss B. H. Lowe, to whom we wish to express our thanks.

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## THE PRESENT STATUS OF THE FUNCTIONS OF THE THYROID GLAND

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We probably possess a more detailed knowledge of the embryology, anatomy, physiology, chemistry and pathology of the thyroid than of any other gland. But as regards its interrelations with other tissues,—a vastly greater and more important field,—it can truthfully be stated we are only at the beginning of any definite knowledge.

No attempt will be made to refer to or review all the literature relative to thyroid physiology that has appeared during the last decade. Excellent reviews of this type are available in an article by Vincent (1) in 1911 and in certain textbooks, notably Biedl's (2). Rather a critical summary of the present status of certain phases of our knowledge of this gland and some of the important steps involved in acquiring it as they appear to the author will be attempted. Owing to the recent great popular interest in endocrinology (one is tempted to say endocrinology) the thyroid gland has suffered with the rest, though perhaps less than its sister glands, from loose speculation. This, however, is only because we possess a greater number of unchallengeable facts relative to the thyroid.

**ANATOMY.** *a. Ancestry and embryology.* Owing to the survival of one class of vertebrates—the Cyclostomes—it has been possible to establish the ancestry of the thyroid of all higher vertebrates as a direct metamorphosis of the endostyle organ. The endostyle organ is an elaborate ventral mid-line pharyngeal gland in Tunicates, Amphioxus and Ammocoetes (3). In Tunicates and Amphioxus it opens into the pharynx through a groove extending the full length of the organ (5). In Ammocoetes the opening into the pharynx is reduced to a large duct (4). During the metamorphosis of Ammocoetes the endostyle organ undergoes atrophy with complete loss of three of its specialized types of epithelium including the duct, and the ductless thyroid follicles of the adult are formed from one persisting type of endostyle epithelium (6). These cells sometimes retain their cilia after metamorphosis. The ductless thyroid follicles in Cyclostomes arise solely from the endostyle

organ. Studies in the embryology of the thyroid of fishes, amphibians, reptiles and birds have shown that it also arises solely from a median single ventral tubular downgrowth of the pharyngeal endoderm in or slightly anterior to the first aortic arch (8), (9). This symmetry and uniformity of development was believed to be departed from in mammals owing to the discovery by Stieda (10) of the so-called lateral thyroid anlagen. These lateral thyroid anlagen were believed to give rise to the lateral thyroid lobes and to be developed from the fourth gill pouches, or more accurately in man from the rudimentary fifth. The view that the thyroid in mammals arises from three separate anlagen persists and still appears in many textbooks. Recent studies of the fate of the so-called lateral thyroid anlagen, post-branchial bodies, or better, ultimo branchial bodies, show that they are only atrophic remnants from the fifth pair of gill pouches which, during development, may become attached to or even embedded in the lateral thyroid lobes, but take no part in the formation of thyroid tissue (11), (12). This solution of the origin of the mammalian thyroid makes it possible to interpret many of the pathological changes and developmental defects of the thyroid, and makes the origin and development of this gland uniform throughout all vertebrates (7), (13).

*b. Gross and microscopic.* Morphologically the thyroid is one of the simplest of body tissues and resembles the lung more closely than any other tissue. Indeed, there are many embryological, anatomical physiological and pathological relations between the thyroid and the lungs the study of which has added much to our present-day conception of interrelationships. The thyroid tissue is one of the most labile tissues in the body—capable of rapid overgrowth and of equally rapid involution. Its wide range or cycle of morphological changes makes it possible to detect easily morphological changes which if interpreted in terms of function are but little removed from the normal, but if compared with similar types of morphological changes in other tissues less well endowed with the capacity for growth have frequently resulted in drawing wholly unjustified conclusions regarding the alteration of function.

The thyroid has only one known cycle of cell changes and it tends to repeat this cycle in response to all stimuli involving increased functional activity.

The normal human thyroid weighs between 20 and 25 grams and does not exceed 0.35 gram per kilo of body weight (36), (14). Statistical data indicate that the thyroid is slightly larger in females per unit

of body weight. The gross outline of the thyroid is quite variable, the greatest variation occurring in the isthmus or pyramidal process (16). In the strictly normal human thyroid the isthmus is a band of tissue from 1 to 2 cm. in width and from  $\frac{1}{2}$  to 1 cm. in thickness connecting the two lateral lobes across the trachea anteriorly just below the level of the cricoid cartilage. The presence of a pyramidal process and thyroglossal stalk must be considered as due to incomplete absorption of this portion of the thyroid tract which normally takes place between the fifth and eighth week of fetal life. In severe endemic goiter districts approximately 95 per cent of human thyroids have well-formed pyramidal processes and thyroglossal stalks frequently continuous with the foramen cecum (15). Similar variations are seen in animals; thus, in congenital goiter of dogs and sheep the thyroid lobes are usually joined by an isthmus while normally in these animals the isthmus undergoes absorption before birth.

The gland is invested with an outer fascia which strips readily and exposes a slightly lobulated smooth surface formed by the inner or true capsule. This is thin and translucent. Thickened portions of this capsule (trabeculae) extend into the gland, support the blood and lymph vessels and give it a slightly lobulated appearance (34), (35). The color of the normal thyroid varies from a pale translucent amber red to a bright translucent amber red. The normal gland is of firm consistency and made up of closely packed circular or oval closed alveoli filled with a glairy honey-colored viscid globulin—the so-called colloid, which gives to the thyroid its specific characteristic, chemical as well as physical. The thyroid unit or alveolus is similar in all vertebrates (30), (31), (32). In man these alveoli vary from 0.1 to 0.5 mm. in diameter and are lined with a single layer of low cuboidal epithelium (columnar epithelium always indicates hypertrophy) (17). The older observers (Langendorf (18), Biondi (19), Hürthle (20) and others) recognized two types of gland cell, the so-called chief and colloid cells. The former are more granular while the latter contain in addition vacuole-like globules filled with a thin fluid which some have considered as a thyroid colloid, similar in many respects to that contained in the alveolar spaces (33).

In recent years a great deal of attention has been paid to the finer specialized cytoplasmic structures especially the mitochondria and the reticular material or Golgi apparatus (27), (28), (29). Cowdry (21), (22), (24) has reviewed the literature of both these subjects. Mitochondria (Altmann's granules) are present in all thyroids. They are

very rare in the fetal thyroid and increase with age (23). Their number also varies with the size of the cell. Their lipoidal nature distinguishes them from secretion granules with which they were long confused. They can be correlated with functional activity as well as with cell growth. Bensley noted that the more active the cell the more numerous were its granules. Some authors, notably Goetsch (25), have in addition attempted to establish a relation between the pharmacological activity of the cell's secretion and mitochondria, particularly in exophthalmic goiter. This view has not received much support for the reason that the very actively hyperplastic columnar cells seen in the thyroids of myxedema are equally rich in mitochondria. They seem closely related in the functional activity of the cell but unrelated to the pharmacological value of the cell's secretion. In the thyroid cell, mitochondria are most numerous in the region between the lumen and the nucleus while in ordinary gland cells like the salivary or pancreas these granules are most numerous in the region between the nucleus and the basement membrane. Bensley pointed out that this was probably due to reversed polarity. Recently Cowdry has studied the thyroid cells of the guinea pig, using the reticular material or Golgi apparatus as an indicator of polarity. He found that the reticular material of the guinea pig thyroid cell was located in the region between the nucleus and the base of the cell in about one cell out of every five hundred, i.e., reversed, and accepts Bensley's (26) explanation that it indicates the ability of the thyroid to secrete either toward the bloodstream or toward the alveolar lumen, and this reversed secretion (toward the lumen) comes into play when the thyroid secretion is being produced in excess of the body needs. Reversed polarity has been observed only in the thyroid gland and as the ancestral thyroid (endostyle organ) was an external secreting organ it suggests that the reversed polarity is a relatively recently acquired characteristic to meet a change in function.

Lymphoid tissue, represented by scattered small foci in the stroma, is normally present in the thyroid (37). Under certain conditions associated with general overgrowth or persistence of lymphoid tissue, as in status lymphaticus, Addison's disease and exophthalmic goiter, this lymphoid tissue may undergo an extraordinary hyperplasia with the development of well-formed germinal centers.

Accessory thyroid tissue other than that found along the thyroglossal tract occurs with great frequency. In dogs and cats accessory masses may be demonstrated in upwards of 90 per cent. The most frequent

sites are in the thymus gland and in the region of the arch of the aorta.

In man there are normally small groups of undeveloped thyroid cells lying in the stroma between the alveoli. These have been spoken of as cell rests and their relation to the development of thyroid adenomata was first pointed out by Wölffler (43). It is believed that the thyroid anlage is capable of and actually produces during embryonic life many more cells than are usually required for functional needs. Under ordinary conditions, as in the case of striped muscle fibers during fetal life these thyroid cell rests undergo gradual absorption beginning in intra-uterine life and continuing after birth. On the other hand, in the presence of a stimulus for increased thyroid activity, these undeveloped rests respond with growth and become the adenomata which are almost universally present in and an integral part of endemic human goiter. Thyroid adenomata are exceedingly rare in the lower animals.

These adenomata are highly variable in size, number and structure. One recognizes types of adenoma composed of closely packed small undistended alveoli—so-called fetal adenoma, and also types with well differentiated large colloid-containing alveoli and finally all gradations between these. Morphologically different types may be present in the same gland. It is believed these variations in morphology depend upon *a*, the stage of differentiation of the cell rest from which the adenoma arose; and *b*, the degree of differentiation occurring during its growth and involution. Adenomata are capable of taking up iodine from the circulation and of elaborating the iodine-containing hormone, thus differing sharply from thyroid carcinoma. The more differentiated types as regards evidence of functional activity approach that of normal thyroid while the fetal types may or may not be able to take up iodine even after the prolonged administration of iodides (44), (45).

*c. Circulation.* The thyroid has a very large blood supply variously estimated from 3.5 to 5.9 cc. per gram per minute (66), (67). Obviously in a tissue with such wide variations in functional activity correspondingly wide variations in the blood supply must be present. Control studies should be made with standardized thyroid and the thyroid happens to be the only tissue which at present can be standardized. This is accomplished by iodine administration. The thyroid arteries form rich anastomoses on the surface but none in the depths of the gland (40). Schmidt (38) and Horn (39) have described endothelial buds or "knospen" in the arterioles which may act to reduce the speed of the blood flow by a baffle-board effect. This also reduces the pulse-wave effects which in a gland with such a short and wide capillary

path would otherwise easily pass through to the veins, especially in the marked hyperplasias. The thyroid gland can be perfused readily at a pressure of 15 to 20 mm. Hg. while the kidney requires from 70 to 80 mm. Hg. pressure. The capillary network surrounding each alveolus is comparable to the capillary network surrounding the lung alveolus. The thyroid is also richly supplied with lymphatic vessels which are collected for the most part into two major channels which leave the gland with the large veins (41). The thyroid hormone can pass directly into the blood stream, as has been shown by Rogoff and Goldblatt (42). There is no evidence except the older morphological evidence that it may also be discharged into the lymphatics.

*d. Innervation.* The anatomical studies of Berkeley (46), Anderson (47), Rhinehart (48) and others have shown that the thyroid is richly supplied with nerves, all of which are believed to belong to the sympathetic system. These nerves leave the spinal cord between the second and seventh thoracic segments and pass upward to the middle and superior cervical ganglia from whence they are relayed to the thyroid *a*, directly along the blood vessels, or *b*, indirectly through the superior laryngeal and possibly the recurrent laryngeal nerve. These nerves are distributed both to the perivascular tissues and to the bases of the gland cells—the latter have been recorded by anatomists as possible secretory nerves (56), (56a). The gland is richly supplied with vasomotor nerves both constrictor and dilator (54), (55). The question of secretory nerves has attracted much attention during the last decade and still remains undecided. All the evidence is indirect. Asher and Flack (49), (50) first showed that in rabbits the blood pressure response to a given dose of adrenalin was greater after electrical stimulation of the superior laryngeal nerve with intact thyroid than before such stimulation. They also showed that after thyroid removal, stimulation of the superior laryngeal nerve did not modify the blood pressure response to a similar dose of adrenalin. Oswald (51) obtained similar results by injecting iodothyreoglobulin instead of stimulating the thyroid nerves. Levy (52) has confirmed Asher and Flack's work on cats. Epinephrin produces all these effects and also markedly raises the heat production in the absence of the thyroid gland. The difference is only one of degree. Von Cyon (53) has criticized Asher and Flack's work by pointing out that where blood pressure is used as an indicator, many factors particularly the degree of anesthesia must be carefully controlled, and also one must distinguish between goiterous and non-goiterous rabbits for this kind of work. Rahe, Rogers, Fawcett, Beebe and others



(58), (59) have shown that the iodine content of the thyroid may be reduced by prolonged faradic stimulation of the cervical sympathetic. Cannon and Cattell (57) showed that there was an alteration in the electrical potential of the gland on stimulating the cervical sympathetic. No such effect was observed when the vagus or sciatic nerves were stimulated or when the systemic blood pressure was changed. They interpreted this as evidence of secretory innervation.

All these methods are highly indirect and complicated and the results are not susceptible of complete analysis at present. Other more direct proof must be offered before one can accept the doctrine of secretory nerve control of the thyroid secretion. That some sort of nervous control whether secretory or regulatory exists is probable on the grounds of analogy. Whether this regulation is dependent on specific nerves or on specific chemical changes acting through a more general regulatory nervous mechanism is still to be demonstrated. On the other hand, there is very direct evidence that specific nerve endings are not necessary for thyroid tissues to show many evidences of variation in secretory activity. Thus, by autografting the thyroid in widely separated parts of the body it has been shown that such transplanted thyroid wherever located shows chemical and morphological changes paralleling those of the non-transplanted tissue (60). If the transplant is undergoing hyperplasia, the non-transplanted portion is also undergoing changes similar in nature and degree. The administration of iodine inhibits hypertrophy alike in the transplanted and non-transplanted thyroid. In 1914 Cannon (61), utilizing Langley and Anderson's (62) method of anastomosing motor and sympathetic nerves, united the anterior root of the phrenic with the peripheral end of the cervical sympathetic in the cat and reported the occurrence of symptoms closely resembling exophthalmic goiter—tachycardia, emaciation, increase in metabolism to plus 100 per cent. He ascribed these phenomena to the bombardment of the thyroid with impulses discharged through the phrenic stump. These results have neither been confirmed by others (63), (64), (65) nor repeated by Cannon.

PHYSIOLOGY. *a. Effects of thyroid removal.* Our knowledge of the physiology of the thyroid may be said to have begun with Gull's report in 1874, *On a Cretinoid State Supervening in Adult Life in Women* (74). Prior to its publication, the function of the thyroid was either speculative—that it aided in the formation of erythrocytes, that it acted as the vascular shunt for the cerebral circulation, that it neutralized toxins, that it served only to give form to the neck, etc.,—or was hopelessly

confused with the function of the parathyroids. It was not until Gley in 1891 (75) rediscovered the parathyroids that any real differentiation of the functions of the thyroid and parathyroids was possible, and it was some twenty years after this that their functions were finally separated to the satisfaction of all workers.

Independent observations reported by the Brothers Reverdin in 1882 (76), and more clearly by T. Kocher in 1883 (77), on the effects of total thyroidectomy in man for goiter established the first experimental confirmation of Gull's clinical-pathological observations. Some of these operated human cases developed parathyroid tetany and died, while others developed during the next thirty to sixty days a cachexia which these surgeons recognized as similar to that described by Gull. The Reverdins designated the symptoms complex as operative myxedema (Ord (78) in 1878 having given the name myxedema to the condition described by Gull because his chemical examinations indicated there was an increased mucin formation in the thickened subcutaneous tissue) while Kocher called it *cachexia strumapriya*. Horsley (79), (80) in 1884, working with monkeys, observed a few instances of cachexia strumapriya; most of the monkeys developed tetany. Other observers carried out similar experiments on rabbits, sheep, goats, dogs, cats and guinea pigs. Those working with rabbits claimed that thyroidectomy was usually without noteworthy effect, while those working with carnivora usually obtained parathyroid tetany. The experimental thyroidectomies before 1891 in general added confusion rather than facts to the function of the thyroid. Since 1891 many species of mammals have been subjected to thyroidectomy using standard surgical technique and excluding the parathyroid factor. The most striking effect of thyroidectomy is a reduction in the total metabolism. In cats and rabbits this decrease begins usually in from six to eight days after thyroidectomy and reaches its lowest level between the twentieth and thirtieth day (81), (82). This low level of metabolism may be maintained for years (rabbit) or as accessories develop the metabolism may gradually rise to normal. In these animals the average maximum reduction in metabolism is around 35 per cent to 40 per cent, which corresponds closely to that observed in the severest forms of human cretinism and myxedema and may be designated as the myxedema level.

While qualitatively the symptoms following thyroidectomy in both young and adult animals are similar, the visible manifestations are strikingly more prominent in animals thyroidectomized during the period of growth. Adult herbivora like the rabbit, sheep or goat may

show very little change clinically beyond a dryness and thickening in the skin, thinning of the hair, a gain in weight and a lowering of body temperature. This was observed by the earlier workers. Heat production measurements in these animals, however, show the usual marked decrease. In the young there are in addition the gross manifestations of stunted physical, mental and sexual development.

With a knowledge of the frequency and functional importance of accessory and aberrant thyroid tissue, the writer believes that in the adult animal (sheep, rabbit, cat) the thyroid is not essential for vegetative life, while in the young it is only indirectly essential in that it is necessary for growth and development. The thyroid is an organ acquired late in the development of animal life, present only in the higher Chordates, and all we know of its function indicates that it provides the means for maintaining a higher level of metabolism and for varying its rate.

*b. Biochemistry.* The next most important advance in thyroid physiology was the demonstration in 1891 by Murray (82a), of the remarkable therapeutic effect of the injection of a glycerol extract of fresh sheep's thyroid in cases of Gull's disease. This was quickly followed by the independent announcements in 1892 by Howitz (83), by Mackenzie (84) and by Fox (85), that thyroid either fresh or dried or boiled was equally efficacious when fed by mouth. Emminghaus and Reinhold (86) in 1894 showed that thyroid feeding also caused a marked reduction in the size of goiter. These discoveries of the therapeutic effects of thyroid feeding also mark the beginning of thyroid biochemistry. The names of Hutchinson (87), (88), (89) in Great Britain, Frankel (90) in Austria, Baumann, Roos (91), Oswald (92) and Dréchsel (93) are most closely associated with the biochemical work of this early period which culminated in the announcement in 1895 by Baumann (94), (95), (96) of Freiburg that iodine in a rather firm organic combination was a normal constituent of the mammalian thyroid. He obtained a substance by acid hydrolysis which he named "iodothyrene." This substance was later put on the market by a pharmaceutical firm under the name of "thyroidin." The substance obtained by Baumann was a brown amorphous powder insoluble in water and acids, slightly soluble in alkalis, gave no protein reactions, contained 0.4 to 0.5 per cent P. and as high as 9.3 per cent iodine. Later work has shown that this method of hydrolysis (10 per cent  $H_2SO_4$ ) partially destroys the specific iodine compound. Baumann and his pupils, Roos and Goldman (97), showed that iodine was present in the

mammalian thyroid in very variable amounts and that feeding iodine increased the store. Oswald (98), (99), in 1899, observed that the iodine was contained in the colloid, and that the colloid of the thyroid was mainly globulin, and introduced the terms thyreoglobulin and iodothyreoglobulin. He showed that the iodine content varied in general with the amount of visible colloid in the glands, but that hyperplastic glands could be rich in globulin and iodine-free. The relation of iodine to the structure of the thyroid has been particularly studied by Marine and Williams (100) and Marine and Lenhart (101). These studies have cleared up the controversy that had developed concerning the fundamental importance of iodine in thyroid physiology, because many workers noting the absence of iodine in the thyroid in certain conditions still claimed it was only an accidental constituent probably excreted into the thyroid as a waste product. Much of the earlier work claiming the absence of iodine in the thyroid was, of course, due to faulty methods of chemical analysis. The final results in all of this work showed that the iodine store in the thyroid varies in general with the amount of stainable colloid, inversely with the degree of active hyperplasia and in the extreme degrees of active hyperplasia seen in cretinoid states in man and animals the iodine store may be entirely exhausted. In the following table the relation of iodine to histological structure as found by Marine and Lenhart are given:

	NORMAL	EARLY HYPERPLASTIC STAGE	MODERATE HYPERPLASTIC STAGE	MARKED HYPERPLASTIC STAGE	COLLOID OR RESTING STAGE
Man.....	2.17*	0.88	0.71	0.32	2.00
Dog.....	3.32	0.62	0.37	0.11	1.99
Sheep.....	2.47		0.40	0.01	3.00
Ox.....	3.46	1.65		0.19	
Pig.....	2.51	1.10			2.35

\* Iodine in milligrams per gram dried gland.

Earlier workers reported discordant results regarding the presence of iodine in the fetal thyroid (102). Fenger (103), (104), using standard methods of analysis, showed conclusively in a large series of animals that iodine is present in the fetal thyroid of cattle, pigs, sheep and man. In cattle it is present as early as the third month of intra-uterine life, that is, six months before birth. The iodine content gradually rises with the increasing age of the fetus and shows the same variations dependent upon structure as seen in extra-uterine life. The writer has

made similar observations on a large series of fetal thyroids of dogs. The iodine store in the thyroid shows striking seasonal variations, being highest in the early autumn (October) and lowest in the early spring (April) in this latitude (Seidell) (105), (106). The thyroid has an extraordinary affinity for iodine (107), (108). This was first observed by Baumann in 1895, though iodine has been knowingly used in the treatment of goiter since 1820 (Coindet) and unknowingly throughout many parts of the world, civilized and uncivilized, for unknown centuries. Iodine given to pregnant mothers is also readily stored in the fetal thyroid. The amount of iodine taken up by a given thyroid varies with the degree of active thyroid hyperplasia. The maximum store per gram being relatively constant, for most mammals thus far examined averaging between 5 and 5.5 mgm. per gram of dried thyroid (109). The minimum amount necessary for the maintenance of normal gland structure is likewise relatively constant, averaging about 1 mgm. per gram of dried substance (110). The average normal iodine content for human thyroid is around 2 mgm. per gram of dried substance and the maximum total store of iodine in a strictly normal human thyroid does not exceed 25 mgm. (111), (112), (113), (114). These facts are of the utmost importance in the practical application of iodine to the prevention of goiter.

Perfused surviving thyroids show the same marked ability to take out and store iodine from the circulating fluid as is seen in the thyroid *in situ* (115), (116), (122). It has been shown that the iodine content of the thyroid of a dog may be increased several hundred per cent within five minutes after the injection of 50 mgm. of potassium iodide into the femoral vein. As much as 18.5 per cent of a single intake of 38 mgm. (50 mgm. KI) given to a dog by mouth may be recovered from the thyroid whose ratio to body weight was as 1:687. The thyroid stands alone at present among the specific affinities of tissues for inorganic substances.

The older literature contains many reports of the presence of appreciable amounts of iodine in the parathyroids, thymus, pituitary and other organs. Excluding its presence in tissue due to the recent administration or to contact with iodine, active normal tissues other than the thyroid do not contain amounts greater than could be accounted for by its discharge from the thyroid. A great deal of work has been done in the attempt both to isolate and to synthesize the active iodine compound of the thyroid, especially by Oswald (117), Nürnberg (118), Koch (119) and many others (120), (121). Whole proteins—casein, gluten, serum-

albumin and globulin and many amino acids including tyrosin, tryptophane, histidin and phenylanilin have been iodized but none of these were active. Later work, using the tadpole as a test object, showed that iodized blood serum, especially the globulin fraction, has a slight thyroid-like effect (123). In 1916 Kendall (124) reported the isolation of the specific iodine compound in crystalline form which he named "thyroxin." According to his latest report (125) this substance has the empirical formula  $C_{11}H_{10}O_3NI_3$  and structurally is trihydro-triiodo-oxy-beta indolepropionic acid. This substance in the purest form yet obtained contains 65 per cent iodine, has a melting point of around 250 and crystallizes in sheaves of needles. Kendall has shown that this substance produces the same pharmacological effects as whole thyroid. Kendall also showed that iodine is present in the thyroid in both an active and inactive form (126). Taking advantage of the extraordinary affinity of the thyroid for iodine and of the Gudernatsch tadpole test, Marine and Rogoff (127) carried out experiments to determine the rapidity of the production of active thyroid iodine. Differences in pharmacological activity of the thyroid were detectable in eight hours after intravenous injection of 50 mgm. KI and the differences in activity were quite marked after thirty hours. These observations indicate that while the storage of iodine is instantaneous the formation of thyroxin is a relatively slow process.

In 1895 Magnus-Levy (128), (129) reported in Gull's disease that the respiratory exchange was markedly decreased below normal and that in Graves' disease it was notably increased. He also demonstrated that feeding thyroid to cases of Gull's disease markedly increased their respiratory exchange and the excretion of urinary nitrogen. Friedrich Müller had recognized the increased nitrogen excretion in Graves' disease in 1893 (130). These discoveries by Magnus-Levy are the most important contributions to the pharmacology of thyroid substance and among the most important contributions to our knowledge of thyroid physiology. The most characteristic pharmacological action of thyroid or of its isolated active substance, thyroxin, is an increase in total metabolism (131), (132), (133), (134), (135), (136), (137). Its action is in general proportional to its iodine content as determined either by measurements of heat production, nitrogen excretion or the Gudernatsch tadpole test (138) (the most sensitive test yet developed for thyroid). In tadpoles thyroid substance causes a rapid loss in weight associated with metamorphosis in a few days. This is proportional to the active iodine (139). Some have considered that the action

of thyroid on tadpoles was a specific stimulus to differentiation. All the phenomena observed may be explained on the well-known action of the thyroid in accelerating metabolism and the apparent specificity does not depend on a new specific action of thyroid but on its application to a living organism at a specific period in its development (140). The acetonitrile test of Hunt and Seidell (141), (142), (143) is not specific for thyroid activity, since while thyroid feeding increases the resistance of white mice to acetonitrile poisoning it decreases it in rats and guinea pigs. Further, removal of the thyroid does not alter the response in mice and the blood of thyroidectomized animals also protects. In man, Plummer (144) has roughly estimated that for the normal individual approximately 1 mgm. of thyroxin daily is sufficient for normal metabolic activity.

The effect of thyroid on the heart and circulation has been particularly studied by von Fürth (145), (146), von Cyon (53) and Oswald (147). Aqueous extracts of the whole gland injected intravenously caused the usual lowering of blood pressure, while purified solution of iodothyreoglobulin causes only a slight lowering of blood pressure but the heart rate is notably increased after a latent period. Oswald believes that thyroid increases the irritability of all sympathetic nerve endings. The thyroid has no specific effect on blood coagulation. In Graves' disease the coagulation time is usually prolonged but attempts to establish a thyroid relation have been negative (148), (149), (150). The relation of the thyroid to immunity has received a great deal of attention and the literature is confusing and contradictory. In general it has been found that hemolysin and agglutinin formation are higher in thyroidectomized than in control rabbits, while antitoxin (diphtheria) formation is lower in thyroidectomized animals (dog, horse and rabbit) (151), (152), (153), (154), (158), (159), (160). Fjeldstadt (155) in eighteen thyroidectomized rabbits found no increase in agglutinin formation. Most observers have reported numerous exceptions to the above general statement except Ecker and Goldblatt (156) who found the hemolytic titer of thyroidectomized rabbits always higher than the controls. It is stated that anaphylactic shock does not occur in guinea pigs if sensitized after thyroidectomy but does occur if sensitized before thyroidectomy (157). At present the results obtained do not warrant any direct association of the thyroid with antibody formation. The reaction to infections as shown by a reduction in iodine store and a tendency to hypertrophy and hyperplasia clearly indicate the thyroid is an important indirect factor in resistance

to infections. The increased heat production in infections is to some extent dependent upon the thyroid.

*c. Regeneration and transplantation.* The mammalian and avian thyroid regenerates rapidly after partial removal. Two major factors—the amount removed and the administration or the withholding of iodine, and probably many minor factors—age, diet, species, determine the degree of regeneration (70). In the dog, if one removes three-fourths of the gland, ordinarily regeneration occurs in the remaining fourth, but if small amounts of iodine are given, such regeneration does not take place. If as much as nine-tenths of the gland is removed, iodine in any amount does not protect against regeneration. Halsted (68) made an extensive study of thyroid regeneration in 1889. Ribbert (69) showed that regeneration may begin within a few days after partial removal and occurs first in the sub-capsular zone. His suggestion that this centrifugal growth is dependent upon a more active blood supply is probably correct. The irregular insular hyperthrophy and hyperplasia often seen in human goiter may be thus explained. Anatomically and chemically the thyroid changes in regeneration are identical with those occurring in the spontaneous hyperplasias of simple goiter and are controllable by the same methods, i.e., cellular hypertrophy and hyperplasia do not occur until after the iodine store falls below a given level (0.4 mgm. per gm. dried) (70).

Transplantation of the thyroid has been extensively studied by Cristiani (71), L. Loeb (72) and his co-workers, and by Manley and Marine (73). Thyroid tissue autografts readily in any part of the body and shows all the chemical and morphological reactions seen in the non-transplanted tissue. Growth of the transplant varies inversely with the degree of thyroid insufficiency created in the host. The administration of iodine or desiccated thyroid inhibits the growth of thyroid transplants. In much of the older work on transplantation, attempts to transplant large pieces, even whole glands, were failures. As only the peripheral layer of not more than four to six cells in thickness survive, the ideal transplant is a slice of tissue about 50 microns in thickness laid on some flat surface, as the subcutaneous tissue or the sheaths of muscles. The frozen thyroid tissue of rabbits also transplants readily (Manley and Marine). Many such experiments were made where the tissue was frozen with carbon dioxide from one to five minutes. The temperatures reached were not measured. Homeografts are rarely permanent. Barring technical errors, they all “take” but begin to undergo absorption as early as the seventh or eighth day.



Some animals destroy initial homeografts much more slowly than this, indicating that there are different degrees of foreignness of the transplanted proteins in animals as well as in man. In man, by transplanting within the same blood group it is probable that the average life of homeografts might be somewhat prolonged. But there are such great differences within a given group which cannot be detected by the usual hemolysin or agglutinin tests, that permanent value from homeo-transplantation is at present hopeless and must continue to be until some means is discovered to overcome the foreign protein reaction to the grafted tissue.

Heterotransplantation of thyroid in mammals never succeeds.

*d. Diet.* Diet notably affects both the structure and chemistry (166), (167), (168), (169). Baumann (96) in 1896 and many others (161) noted in dogs that fresh meats caused hypertrophy of the thyroid, while sea fish (cod) increased the iodine store. Watson (162) also found that a meat diet caused hypertrophy and hyperplasia of the thyroid cells in rats. Marine and Lenhart (163) (164), (165) showed that liver, particularly pigs' liver, was the most potent of a great variety of meats in causing thyroid hyperplasia in dogs and cats and also this food was an important factor in the causation of goiter in brook trout. Recent work by McCarrison (170), confirmed by Mellanby (171) showed that fats were even more potent in producing thyroid hyperplasia. McCarrison's suggestion that his effect is in part dependent on an increased bacterial putrefaction in the intestine seems unlikely. As thyroid hyperplasia is secondary to the depletion of the iodine store, these facts indicate that diets rich in proteins and fat increase the rate of discharge of iodine. It seems probable that thyroid activity is more necessary for the oxidation of fats and of proteins than of carbohydrates. Carbohydrate diets do not cause thyroid hypertrophy, as has been shown by McCarrison. Inanition brings about involution of the thyroid, decrease in the size of the epithelial cells and increase in colloid (172), evidence of decreased functional activity.

**INTERRELATIONS.** We are only at the beginning of definite knowledge concerning its functional interrelations with other tissues. During the last decade this subject has become involved in a stupendous mass of ill-advised speculation, exploitation and fiction. Interrelations may be either inhibitory (antagonistic) or augmentory in nature. Sufficient facts are available to indicate that these correlations determine the thyroid's most important effects on nutrition. These effects are brought about by acceleration and inhibition of its functional activity

which in turn are caused by chemical factors, positive or negative, acting through the blood stream either directly on the gland cells or indirectly through nerve impulses. Further, we must recognize that inhibition and acceleration of tissue activity may be brought about by the presence of a specific hormone or by its absence and that apparent acceleration may be an actual loss of inhibition and vice versa.

*Thyroid-Parasex glands.* (*Suprarenal cortex, interstitial and luteal cells.*) The relation of the thyroid to the sex glands was known to the ancients in its crudest external manifestations—the thyroid enlargement with menstruation, puberty, pregnancy and menopause (173). This relationship has passed down to our time with no proved additions to our knowledge concerning it (174). Recently it has been demonstrated that when the suprarenal cortex in rabbits is sufficiently injured as by freezing or by partial removal, a marked chronic increase in heat production usually occurs (80 per cent in a series by Marine and Baumann) (175). This increase usually begins within three to six days after the suprarenal injury and may last from two weeks to several months. Heat production may be increased to 60 per cent or more above the normal. On the other hand if the thyroid gland is removed and the metabolism allowed to fall to the myxedema level prior to the injury to the suprarenal cortex, this increase in heat production does not occur (82). Scott (176) has confirmed these findings, using cats. Golyakowski (177) in 1899 in a brief preliminary report observed increased CO<sub>2</sub> output in dogs following ligation of the suprarenal vessels. There is some evidence that the increased heat production is associated with a loss of iodine from the thyroid and recently Black, Hupper and Rogers (178) have published evidence that feeding “suprarenal gland residue” to dogs increased the iodine store of the thyroid. This reaction with increased heat production appears then to be a suprarenal cortex thyroid interrelationship. Our present interpretation is that the suprarenal cortex exercises a regulatory or inhibitory control over thyroid activity and when this is withdrawn the thyroid automatically responds with increased function. It should be pointed out that there is evidence that the suprarenal cortex exercises an inhibitory control over other tissue functions as well—the thyroid suprarenal interrelation, therefore, is not an isolated one. The practical application of these observations may be of great importance; for example the enlargement of the thyroid at puberty, during menstruation, pregnancy and menopause may be thus partly explained. The effect of bacterial toxins in causing thyroid hyperplasia may be in part determined by a primary

injury to the suprarenal cortex. Other well-known facts involving obvious interrelations as, for example, the hypersusceptibility of certain individuals to adrenalin or the hypersusceptibility of certain individuals to desiccated thyroid and thyroxin, probably have as their basis this fundamental thyroid suprarenal cortex interrelationship. Exophthalmic goiter is in some way intimately involved in this interrelation and the popular conception that this disease is a primary thyroid disease must give way to a broader conception in which cortical exhaustion indirectly, and epinephrin stimulation directly, are in my opinion important primary factors in bringing about increased thyroid activity. Enlargement of the suprarenal cortex with an increase in the epinephrin store has been observed following prolonged feeding with desiccated thyroid (179), (180), (181), (182), (183). During starvation, enlargement of the suprarenal cortex has been observed. Both of these phenomena may be interpreted as an attempt to suppress thyroid activity.

Finally, the normal involution of the suprarenal cortex in infants should be mentioned. This remarkable destruction of the reticular and fascicular zones of the cortex has been observed only in infants and begins during the second or third week of extra-uterine life (183a). The process is initiated as a hemorrhagic infiltration of the two inner zones and goes on to necrosis, destruction and absorption of these layers with collapse and folding of the glomerular zone on to the medulla. The duration of the stages of absorption and healing is indefinite. Some authors estimate it at two to three weeks and other at two to three months. The end result, however, of this destruction is a marked decrease in the volume of cortex so that a child one year old has a smaller total volume of cortex than at birth.

The physiological significance of this rapidly progressive partial destruction of the cortex is unknown. It is not accidental or traumatic. Its occurrence in accessory suprarenals as well suggests that it is a systemic purposeful reaction to meet the altered conditions incident to extra-uterine life. In the light of the relation of experimental injury of the suprarenal cortex in rabbits, dogs and cats to increased heat production, it is suggested that one of the effects of the cortical destruction in infants may be increased heat production through thyroid activation. All that can be said at present is that the cortical injury and increased heat production in infants begin at approximately the same time and parallel each other.

*Thyroid-Chromophil tissue.* Epinephrin injected intravenously causes a marked constriction of the thyroid vessels. An interrelationship of

function was first postulated by Eppinger, Falta and Rudinger (184). They assumed that the chromophil system directly stimulated the thyroid. This conception received experimental support from the work of Asher and his pupils (186), who in 1910 showed that the blood pressure response in rabbits to a given dose of adrenalin was greater after stimulation of the thyroid nerves with intact thyroid than before such stimulation. This has been confirmed from several sources and especially by Cannon and his co-workers. The Goetsch epinephrin test in exophthalmic goiter is a clinical application of this reaction. Oswald has shown that a similar increase in the reaction to epinephrin may be obtained by injecting iodothyreoglobulin instead of stimulation of the thyroid nerves. The nature of this reaction is still in doubt (187), (188). Asher and Flack believe that the thyroid hormone increases the irritability of or sensitizes the tissues innervated by the sympathetic nervous system in some way so that it is more susceptible to stimulation by epinephrin.

*Thyroid-Gonad interrelationship.* Very little is known (185). That there is an important direct relation between some constituent of the gonads, especially in the female, and the thyroid is certain. The exceedingly complex nature of the sex gland has thus far been a perfect barrier to trustworthy experimental investigation. Total removal of the gonads usually leads to a slight depression of the thyroid function (189).

*Thyroid-Hypophysis.* Rogowitsch (190) and others (191) (192), (195), (196) have reported marked enlargements of the anterior lobe and especially the pars intermedia following thyroidectomy—as much as 400 per cent. They interpreted this enlargement as indicating that the pituitary could function vicariously for the thyroid. Subsequent work by Simpson and Hunter (193) and by the author has not confirmed this. In rabbits there is a slight hypertrophy of the anterior lobe, but this is rarely more than 15 to 20 per cent after five or six months. Many investigators have found traces of iodine in both the human and sheep hypophysis—others have failed to find it. Simpson and Hunter (194) showed conclusively that the sheep pituitary contained no iodine even in animals recently fed with this element. Livingston (197) on the other hand has published a few observations indicating that desiccated thyroid protects male thyroidectomized rabbits against pituitary hypertrophy. No pituitary hypertrophy was observed in thyroidectomized female rabbits even without thyroid feeding. Hewitt (198), however, reported that thyroid feeding in white rats caused pituitary

enlargement. The idea that the thyroid and pituitary were functionally related seems to have been suggested by Virchow and was based on the morphological resemblance of the colloid filled follicles of the para intermedia to the thyroid follicle. Acromegaly is usually associated with a slight increase in the size of the thyroid and with an increase in heat production rarely over 20 per cent. None of the facts thus far established suggest any direct functional relation between the hypophysis and the thyroid.

*Thyroid-Thymus.* There is no evidence of any important relation between these two organs despite a relatively large literature dealing with their functional interdependencies (199). There is no doubt that the thymus is usually enlarged or persistent in many conditions in which the thyroid is involved, for example, simple goiter, myxedema, Graves' disease. Asher and Ruchti (200) found no change in the respiratory exchange after thymectomy in rabbits whether performed before or after thyroidectomy. Gudernatsch thought thymus feeding inhibited to some extent the action of the thyroid feeding on tadpoles. Baumann (unpublished) has found that foods enriched by the addition of protein-free nucleic acids of any origin stimulate growth in tadpoles. That there is an important indirect relation between the thyroid and thymus through the sex glands and suprarenals is certain since each of these glands is closely associated functionally with the sex and parasex tissues, and both the thyroid and the thymus are usually affected in conditions involving the suprarenals or sex glands, as for example, Addison's disease, status lymphaticus, castration, Graves' disease, etc.

*Thyroid-Spleen.* Asher and his pupils (201) have recently revived the question of the thyroid-spleen interrelationship suggested by Tauber (202) in 1884. Asher found that splenectomized rats with intact thyroids were less resistant to reduced oxygen pressures than normal rats, or rats with combined thyroidectomy and splenectomy. Splenectomy has been found to slightly increase the respiratory exchange in rabbits but this also occurs when the thyroid is removed.

*Thyroid-Pancreas and Liver.* Falta thought the thyroid and pancreas were antagonistic (203). He stated that an epinephrin injection which in normal dogs caused a marked glycosuria does not produce glycosuria in thyroidectomized dogs. Similar observations were made by Grey and de Sautelle (204) on dogs and by Pick and Pineles on goats. Underhill (205), however, denies that thyroidectomized dogs in which great care has been exercised to preserve the two external parathyroids are less susceptible to adrenalin glycosuria. Thyroid feeding was found

to produce a marked decrease in the diastatic activity of the pancreas of white rats and this was often associated with enlargement of the pancreas (206). Clinicians have reported the frequent association of some of the symptoms of Graves' disease with acute pancreatitis (207). It has also been suggested that the lowered sugar tolerance and glycosuria of Graves' disease might involve a thyroid-pancreas interrelation. The increased alimentary tolerance for glucose in myxedema or after thyroidectomy is of doubtful significance. It may be due to decreased absorption from the intestine rather than to a direct thyroidectomy influence. What evidence there is seems to indicate that any thyroid-pancreas interrelationship is an indirect one and dependent on epinephrin sensitization. Whipple and Christman (208) have shown that thyroidectomy does not influence the excretion of phenoltetrachlorophthalein by the liver.

*Thyroid-Parathyroids.* No interrelation of function is known. The earlier affirmative statements were based on faulty methods and errors in interpretation.

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## OCHRONOSIS

WITH A STUDY OF AN ADDITIONAL CASE \*

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Ochronosis is the name given by Virchow in 1866 to a condition characterized by the pigmentation of the cartilages, ligaments, tendons and of the intima of the large blood vessels of the body. In this first reported case the pigment deposits appeared light gray, brown and, in places, black. On thin section, however, the pigment was everywhere found to be yellow or yellow-brown and for this reason the condition was called ochronosis.

Since then, forty additional cases have been studied. From the observations made it may be stated that ochronosis is a condition dependent on a disordered metabolism of phenol or some of its derivatives; characterized by a pigmentation of the cartilages, fibrocartilages, fibrous tissues and epidermis, as well as of areas of degeneration, notably atherosclerotic plaques, albuminous masses and concretions. A further characteristic is the presence of a dark urine due to alkapton, derivatives of phenol or to melanin.

The cases of ochronosis may be divided into: (a) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of homogentisic acid; (b) those due to the circulation in the blood of certain aromatic compounds with the excretion in the urine of melanin; (c) those due to the circulation in the blood of certain aromatic compounds following the external use of phenol.

The metabolic disorder responsible for the ochronosis in the first group is a congenital one and characterized by an alkaptonuria. More than one-half of all the ochronosis cases observed are in this group. The metabolic disorder responsible for the ochronosis in the second group results in an excretion in the urine of melanin. Only a few of the ochronosis cases are in this group. The metabolic disorder responsible for the ochronosis in the third group is an acquired one dependent on the prolonged external use of phenol. Eleven of the ochronosis cases observed are in this group.

Twenty-two of the cases in the literature are females; nineteen are males. The average age of the patients at the time of diagnosis was about 51 years. The youngest patient was 23 years of age. There

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\* From the Montefiore Hospital for Chronic Diseases.

\* Part of the expenses of this publication were defrayed from a fund left by the late Dr. H. S. Oppenheimer.

is a tendency for this condition to occur in families where there has been inbreeding.

The diagnosis offers no difficulty. The cartilages of the ears and nose have a bluish tint. The fibrous tissue, especially about small joints, has a bluish gray appearance. There may be dark pigment deposits in the sclerae and patches of pigmentation of the skin. There is an excretion of dark urine or urine which turns dark on standing, due to the presence of alkapton body or derivatives of phenol, rarely of melanin. The pigment may be excreted to some extent by sudoriferous and ceruminous glands.

The most frequent complications in ochronosis are: (a) deforming arthritis of the spine or larger joints, and (b) cardiovascular lesions.

#### HISTORICAL RÉSUMÉ

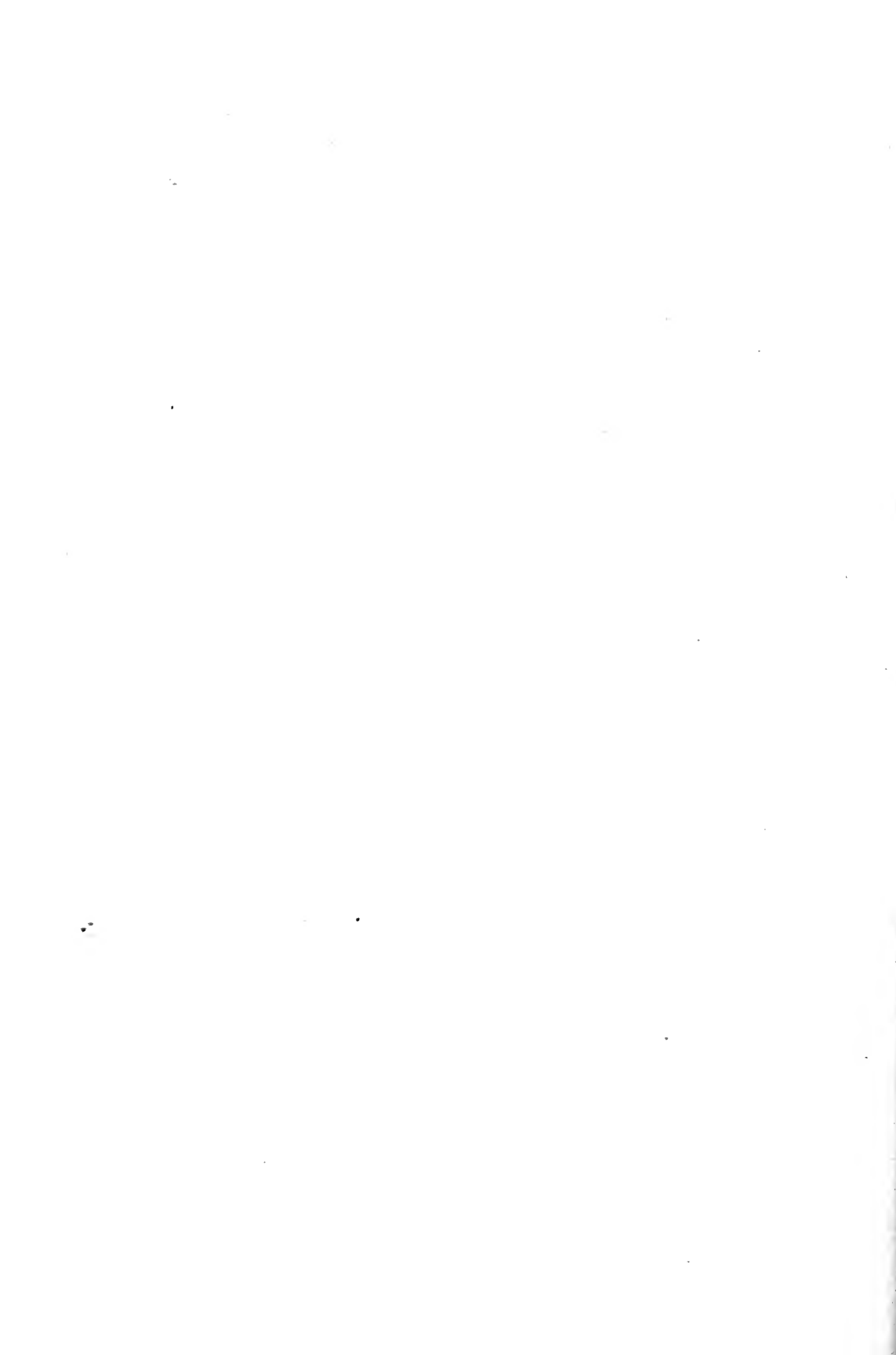
1. *Clinical*.—The early cases of ochronosis were recognized clinically by the pigmentation of the external cartilages. In 1892 V. Hanseman reported a case in which dark urine was passed. Examination of this urine was negative for alkapton body and melanin. In 1902 Albrecht and Zdareck, reporting the seventh case in the literature, called attention to the association of ochronosis with alkaptonuria. In 1904, Osler likewise reported two cases of ochronosis with associated alkaptonuria. No further observations on the nature of the process were recorded until Pick reported a case of ochronosis undoubtedly due to the prolonged external use of phenol. From his chemical study in cases associated with alkaptonuria and in one following chronic phenol poisoning, Pick concluded that in the ochronosis of endogenous origin (congenital, associated with alkaptonuria) a melanin is formed by the action of an enzyme on circulating homogentisic acid and tyrosin, and that in the exogenous form (due to phenol poisoning), a melanin is formed by the action of an enzyme on circulating hydroquinone and pyrokatechin. This explanation of ochronosis, advanced by Pick in 1906, has received no appreciable modification since. In 1908 Gross and Allard reported a case of ochronosis with alkaptonuria in which there was a deforming arthritis of the larger joints. Contrary to Virchow's belief that the pigment was deposited in the inflamed cartilage of the affected joints, they maintained that these arthritic changes were specifically due to the irritation of the deposited pigment. More recently, Söderbergh<sup>1</sup> called attention to a deforming arthritis of the spine in four cases of ochronosis with alkaptonuria. Attention has also been called<sup>2</sup> to the frequent association of cardiovascular lesions with ochronosis and it has been suggested that these changes, like the arthritic ones, are primarily dependent on the metabolic disorder.

1. Söderbergh: Nord. med. Arch. **48**: Nos. 3 and 4, 1915.

2. Beddard: Quart. J. M. **3**:329, 1909.



Moderate ochronotic pigmentation of ears, eyes and axillae; tracheal and bronchial cartilages.



The accompanying table based on Kolaczek's <sup>3</sup> tables shows the frequency of cardiovascular and arthritic changes in the various groups.

CLASSIFICATION OF OCHRONOSIS CASES WITH ASSOCIATED LESIONS

Group	Reported by	Age, Yrs.	Sex	Patho- logic Exami- nation	Arthritis	Cardio- vascular Lesions
a. Carbolic acid	Plek, 1906.....	47?	F	Yes	+	+
	Pope, 1906.....	41	F	Yes	meager des	—
	Græffner, 1907.....	59	F	No	—	—
	Reld, 1908.....	68	F	No	—	—
	Poulsen, 1910.....	55	F	No	—	+
	Poulsen, 1910.....	44	M	No	?	+
	Poulsen, 1910.....	43	F	Yes	—	+
	Beddard, 1910.....	50	F	No	—	—
	Andrews and Branson, 1910 (Kents), 1910.....	69	M	Yes	—	+
	Beddard and Plumtree, 1911.....	73	M	Yes	+	+
	Vogelius, 1914.....	63	F	No	+	—
	Total, 11	Average age.....	52.45	8 F 3 M	5	9 + 2 ?
b. Alcaptonuria	Osler, 1904.....	57	M	No	—	+
	Osler, 1904.....	49	M	No	—	—
	Ogden, 1895 and 1904.....	45	M	No	—	—
	Allard and Gross, 1907 n 1908, Landols, 1908.....	46	F	Yes	+	—
	van Amstel, 1910.....	42	F	No	—	?
	Poulsen, 1910.....	56	F	No	+	—
	Poulsen, 1910.....	19	F	No	+	+
	Poulsen, 1910.....	35	M	No	—	—
	Poulsen, 1910.....	68	M	No	+	—
	Poulsen, 1910.....	61	M	No	+	—
	Kolaczek, 1910.....	44	F	Yes	+	—
	Kolaczek, 1910.....	35	F	No	—	—
	Kolaczek, 1910.....	30	F	No	—	—
	Poulsen, 1912.....	23	M	No	—	—
	Jantke, 1913.....	54	F	.....	+	+
	Umber, 1913.....	51	F	.....	+	+
	Umber, 1913.....	59	M	.....	+	+
	Söderbergh, 1915.....	42	M	.....	+	—
Total, 18	Average age.....	47	9 F 9 M	2	9 +	3 + 1 ?
c. Probably alcaptonuria	Albrecht, 1902.....	47	M	Yes	—	?
	Clemens and Wagner, 1907-8.....	31	M	Yes	—	+
Total, 2	Average age.....	49	0 F 2 M	2	0	1 + 1 ?
d. Melanuria and probably alcaptonuria Total, 1	Poulsen, 1910.....	63	F	Yes	+	+
e. Melanuria no alcaptonuria	Hecker and Wolf, 1899.....	73	M	Yes	+	+
	Oppenheimer, Janney, Kline, 1916.....	40	M	Yes	+	+
Total, 2	Average age.....	56.5	0 F 2 M	2	2	2
f. No alcapton- uria and no melanuria Total, 1	Hanseman, 1892.....	41	M	Yes	—	+
g. Urine not ob- tained or not tested	Virehow, 1866.....	67	M	Yes	+	+
	Bostroem, 1891.....	44	F	Yes	+	+
	Helle, 1900.....	36	F	Yes	—	+
	Helle, 1900.....	52	F	Yes	—	+
	Wagner, 1904.....	67	F	Yes	—	+
	Heymann, 1913.....	55	M	Yes	..	+
Total, 6	Average age.....	58.5	4 F 2 M	6	2	6
Total cases, 41	Average age.....	51	22 F 19 M	19	16 + 2 ?	19 + 2 ?

In the forty-one cases of ochronosis a chronic arthritis of the larger joints or spine has been noted in sixteen. The associated arthritis has been more frequent in the ochronosis with alkaptonuria.

Cardiovascular changes have been noted in nineteen of the forty-one reported cases. These occurred in about equal frequency in cases with alkaptonuria and in cases following phenol poisoning. Not only was there extensive pigmentation of the intima and endocardium in these cases, but also not infrequently a serious chronic valvular disease.

2. *Pathologic.*—In 1866 Virchow reported on a necropsy in a male, aged 67, with an aneurysm of the ascending arch of the aorta, head

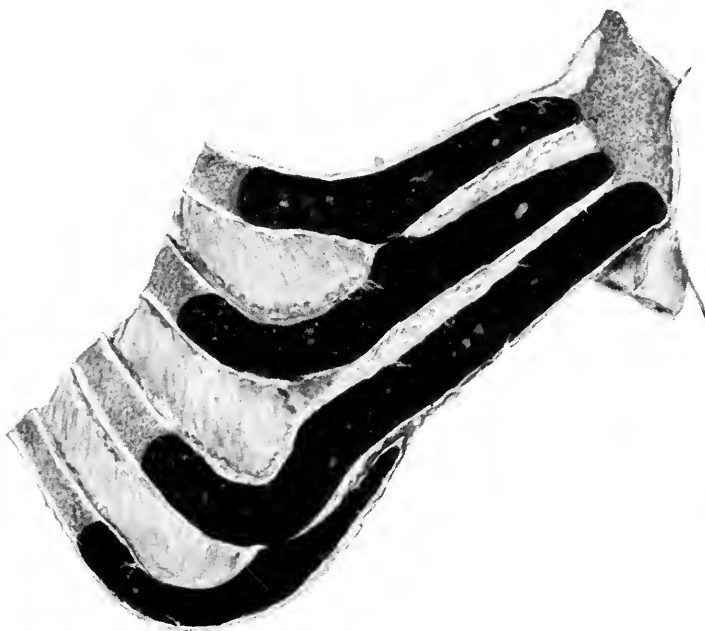


Fig. 1.—Intense ochronotic pigmentation of costal cartilages.

injury and terminal anasarca. The striking lesion, however, was the intense pigmentation of all cartilages and fibrocartilages, with pigmentation to a less extent of ligaments, tendons, perichondrium and periosteum. In this first case there was also some pigmentation of the intima of the larger vessels, especially the aorta, with intense pigmentation of the sclerotic patches in this vessel. The intensely pigmented areas were black or bluish black. The pigmentation of the tracheal cartilages was ochre colored. Histologically, the pigment everywhere was brown or ochre colored, hence the name, ochronosis. Examination of the pigment in this first case by Kühne showed an organic pigment having a definite similarity to hematin derivatives.



Virchow suggested that in ochronosis there is an imbibition from the blood of hematin derivatives occurring in areas poor in vessels and nerves but exposed to irritation. He thought that the process was analogous to the physiologic pigmentation of the rete malpighii, the hair and the choroid and depended on a similar relationship. Furthermore, he believed that there were certain conditions of the cartilages and ligaments which might be considered lower grades of ochronosis. He had occasionally observed that the semilunar plates of the knee joints in old people had a dark yellow or brown appearance and the costal and bronchial cartilages a dark yellowish brown color. In these

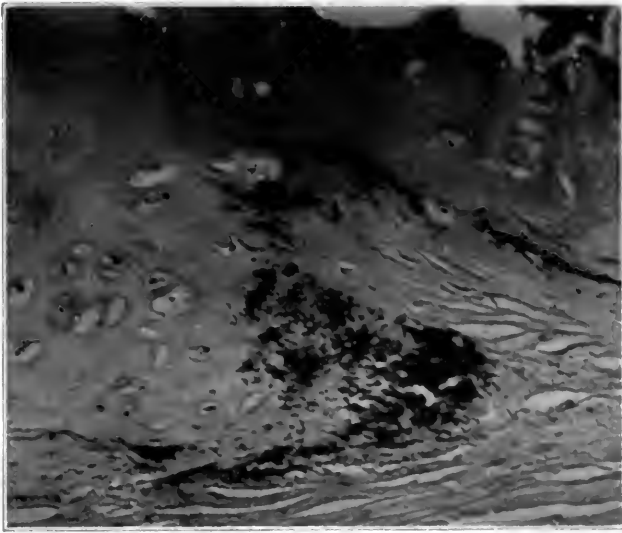


Fig. 2.—Diffuse ochronotic pigmentation of cartilaginous matrix of costal cartilage with granular ochronotic pigment in perichondrium.

instances also, the pigment was deposited in the intercellular substance and was quite homogeneous and diffuse.

Virchow, in this first case, observed changes in the larger joints, particularly the knees, similar to those in arthritis deformans. The deposition of the pigment in these irritated areas gave additional proof to him of his theory, mentioned above. In this first report, no mention of the appearance of the kidneys is made and no mention is made of granular ochronotic pigment.

In concluding his article, Virchow states: "I believe, therefore, that the case here presented, because of the intensity of the pigmentation, was only an excellent example of the more frequent ochronosis."

Hanseman<sup>4</sup> observed diffuse and granular ochronotic pigment in the tissues. In regard to the pigment he states that it is produced in soluble form in the body and in this form absorbed and fixed by certain tissues having but little metabolic activity and in other places changed by cells to granular pigment.

The classical paper on ochronosis is that by Poulsen,<sup>5</sup> who studied ten cases clinically and two after necropsy. He described the pathologic changes as follows:

In all cases one finds a yellowish or brown melanin-like pigment which at times is granular, at times stains the tissues diffusely. This pigment is deposited



Fig. 3.—Diffuse ochronotic pigmentation of intervertebral disc.

principally in the cartilages: costal, those of the air passages and larger joints. Those of the smaller joints are usually unpigmented. The pigment is also present in all the fibrocartilages, such as the intervertebral discs and in the pelvic and intersternal cartilages. The pigment deposition is less intense in the perichondrium, periosteum, tendons, fascias and joint capsules. The bones, although usually unpigmented have shown pigment in a few cases. Outside of the skeleton, the pigment is deposited as a rule only in the endocardium, intima of the larger blood vessels and kidneys; rarely in other places, such as bits of cartilage in the tonsils, in connective tissue of the lung, and

4. Hanseman: 1892.

5. Poulsen: Ziegler's Beitr. z. Path. Anat. **47**: 1910.

thyroid gland, in the fatty tissue about the perichondrium and in the dura mater. The pigment is frequently found in the sclerae, epidermis and in a few cases in the nails. Pigment masses have been observed in the prostate by a few observers, although the authors questioned their specific character. In the cartilage it is deposited in the matrix: the cartilage capsule, and the cells are faintly or not at all colored. Degenerated cells, however, are deeply pigmented. In the other tissues, this pigment is at times in the cells, at times between them. The pigment is excreted in the urine.



Fig. 4.—Ochronotic concretions in prostate.

#### REPORT OF CASE

*History.*—Male, aged 40, presser, admitted to Montefiore Hospital, Nov. 18, 1915.

*Chief Complaints.*—Lancinating pains along spinal column radiating along the lower intercostal spaces to both sides of the abdomen; slight productive cough; occasional hemoptysis; chronic constipation; general weakness; occasional spells of vomiting.

*Family History.*—Negative for consanguineous marriage.

*Past History.*—Occasional attacks of influenza. Frost bite of ears three years ago. Habits: Ten cigarets daily. Eight years before patient's admission to the hospital he was supposed to have had sugar in his urine. Seven years before admission he first noticed peculiar bluish discoloration of the cartilage of each ear.

*Present Illness.*—Eighteen months before admission, while bathing, he experienced sharp stabbing pains along the spinal column, extending forward along the costal spaces to both hypochondriac regions. He left the water at once and went home. The pains, however, continued to grow more and more severe until the following morning when he was unable to resume his occupation. In addition to this sharp pain he noticed stiffness of all the back muscles. He remained at home for the next six months where he was treated with no apparent relief. He then visited Mt. Clemens, Mich. On his return from Mt. Clemens he began to complain of a persistent cough accompanied by profuse greenish-yellow expectoration, blood tinged only for a period of two days,

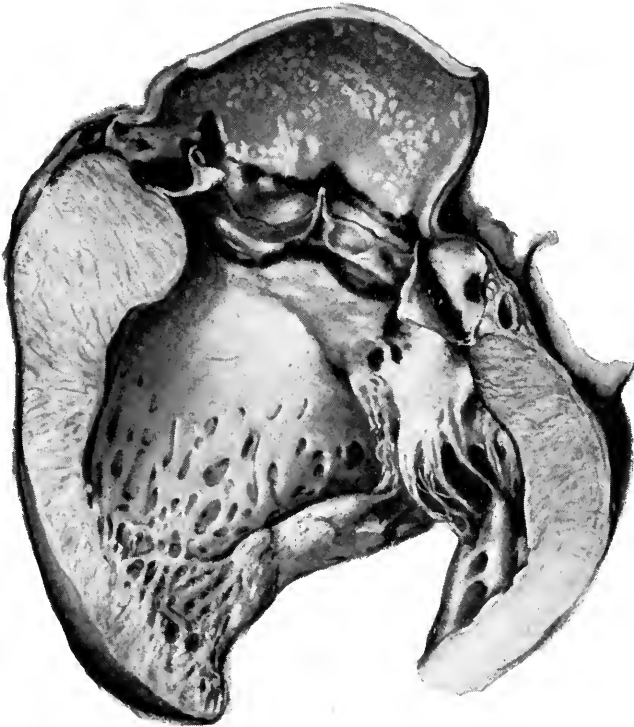


Fig. 5.—Ochronotic pigmentation of atherosclerotic plaques of aortic and mitral valves and in neighborhood of attachment of aortic cusps.

three weeks before admission. In addition he suffered with night sweats and general weakness. He lost twenty-five pounds in weight during the first year of his illness. At the time of admission, cough and loss of weight were almost negligible symptoms.

During the first twelve months of the present illness the patient was treated at various clinics. For the past three months the urine has been reddish-black; the underclothes were often stained black. Associated with this there has been marked polyuria and dysuria. The patient became frightened because of this condition and discontinued taking some white medicine which he was then receiving at the St. Paul's Tuberculosis Clinic and which he felt caused the disorder. He claims that the urinary symptoms mentioned subsided when the drug was discontinued and recurred when the drug was again taken. On being

given various drugs to smell he stated that he was positive the drug he took had the same odor as creosote.

*Physical Examination.*—The patient, an adult male, poorly nourished, appears to be suffering from some chronic illness. Weight, 104 pounds. Gait is very slow and careful. The sclerae of both eyes present a faint bluish tint. In addition there is a wedge shaped bluish-black area of pigmentation of the sclerae to the right of each cornea. Both ears show a peculiar leaden blue discoloration of the cartilage. The same discoloration appears to be present in the nasal cartilage on the right side. Both axillae are diffusely bluish green in color. Some of this discoloration is removable by soap and water and is apparently due to pigment from the sweat and sebaceous glands. There is a pale, brownish diffuse pigmentation of the skin of the neck and temporal regions. The fingers and toes are clubbed; nails pale, not pigmented. Chest: Supraclavicular fossae deep; clavicles exceptionally prominent. Examination of lungs shows few signs at right apex posteriorly suggestive of pulmonary

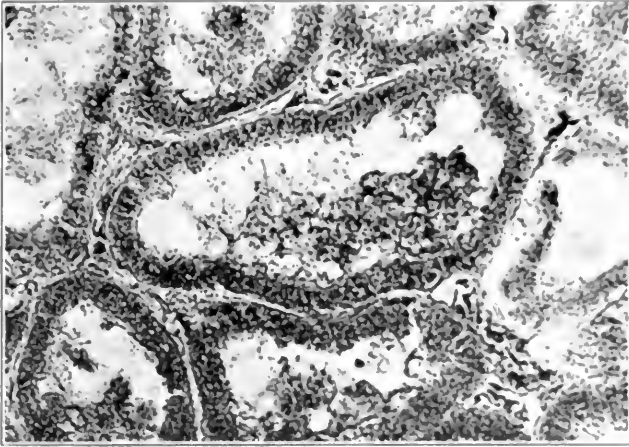


Fig. 6.—Fine ochronotic pigment granules in cells of proximal convoluted tubules of kidney.

tuberculosis. Heart: Not appreciably enlarged. The first and greater part of the second sound at the apex is replaced by a loud harsh murmur transmitted to the axilla. There is some thickening of radial arterial walls; pulse regular; good tension. Liver: Palpable 4 cm. below costal margin in right mammillary line; tender. Extremities: Reflexes increased. Vertebral column: Absolutely rigid, presenting a general bow deformity. Lumbar curve obliterated. There is a great deal of tenderness on any manipulation of either thoracic or lumbar regions of spine.

*Laboratory Findings.*—Sputum: negative on first five examinations. On sixth examination a few tubercle bacilli were found. Blood: hemoglobin, 80 per cent.; leukocytes, 15,000; 85 per cent. neutrophils. Wassermann reaction of blood, negative. Urine: First specimen reddish black when voided, second specimen, when voided, light amber color, turning to yellowish black. Next two specimens were voided black. The following three specimens were smoky but on standing became black. The quantity excreted in twenty-four hours was usually 500 c.c.; specific gravity, 1.010. Albumin, marked trace. Sugar, slight reduction with Fehling's. Examination for bile and blood negative. Occasional

hyalin casts. Chemical analysis of the urine by Dr. Janney showed no homogentisic acid. On the other hand, a pigment was isolated exhibiting characteristics similar to the melanins previously obtained from the urine and tumors in cases of melanosis.

*Roentgen-Ray Examination of the Bones.*<sup>6</sup>—Spine: Almost complete calcification of the intervertebral discs from the first dorsal down. The cervical spine appears practically normal. The lumbar spine shows marked lipping of the lower and upper borders of the bodies of the vertebrae (*Spondylitis deformans*).

Pelvic Bones: Complete calcification of the interpubic disc. Moderate amount of irregular outgrowth along the outer portions of the crests and the ossa ischia.

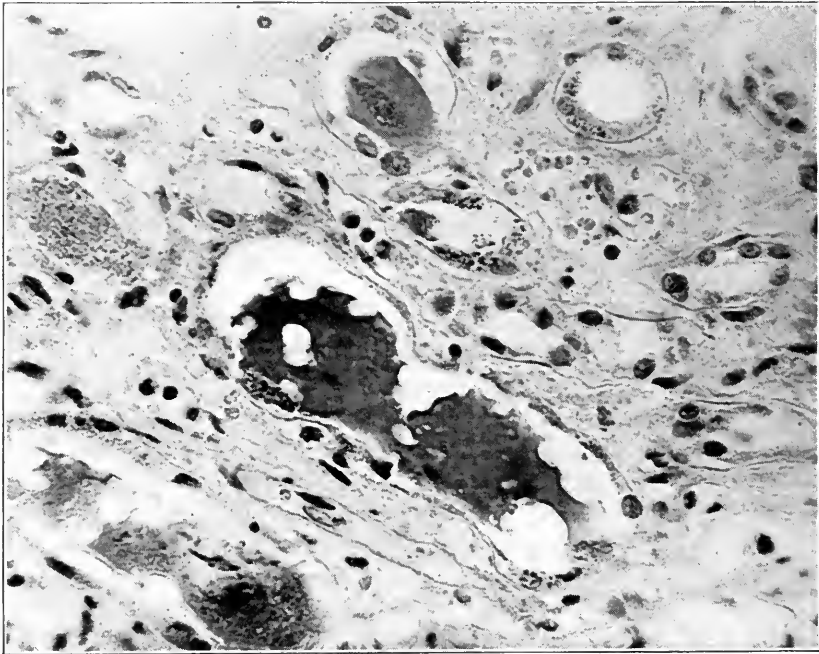


Fig. 7.—Diffuse ochronotic pigmentation of renal casts; granular ochronotic pigment granules in cells of ascending loops of Henle and collecting tubules.

Hips: Marked lipping of the upper portion of the acetabulum. Great amount of calcification around the trochanter major, with some bony excrescences at its base.

Legs: Some calcification along the insertion of the upper portion of the membrana interossea.

Skull: Marked thinning out of both clinoid processes. Complete obliteration of the frontal sinuses.

Shoulders: The joints are free. The upper portions of the humeri show a condition such as we usually see in osteitis fibrosa; rarefaction, lack of clear demarcation between compacta and spongiosa and beginning cystic degeneration.

*Clinical Course.*—The patient vomited persistently, ran an irregular subfebrile temperature until the day of death when temperature rose to 103 F. A half hour after death it was noticed that the entire eyeball, exclusive of the

6. We are indebted to Dr. Th. Scholz for the roentgen-ray report in this case.

cornea, had become brownish black in color and the following day at the necropsy it was noticed that the pigment in the axillae had become much darker than during life.

*Diagnosis.*—The diagnosis of ochronosis in the case was readily made because of the bluish discoloration of the cartilages of the ears and the skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing.

*Chemical Report.*<sup>1</sup>—Examination of the urine in this case was repeatedly negative for homogentisic acid (alkapton body). On the other hand, the pigment obtained from the urine, from a costal cartilage and from the prostate gave reactions for melanin. The pigment from these sources had similar characteristics.

*Pathologic Report.*—Anatomic diagnosis: ochronosis. Pigmentation of costal, tracheal, bronchial, auricular and xiphoid cartilages, intervertebral discs, aorta, endocardium, prostate, skin, sclerae, kidneys; deforming arthritis of larger joints and spine; subacute bacterial endocarditis, mitral valve; subacute glomerulitis; infarct, spleen; healed pulmonary tuberculosis; arteriosclerosis of aorta, pulmonary arteries, mitral valve; pulmonary edema.

*Necropsy Record* (abridged).—Necropsy performed 33½ hours after death. The body is that of a considerably emaciated adult, 153 cm. in length. The skin in general is thin, sallow in appearance. There are tattoo marks on the left forearm. The nails show moderate double curvature. The skin of both axillae, under the arms, has a purplish color. The cartilages of the ear are deep blue in the inner portion, less intensely colored peripherally. The sclerae have a faint blue tinge, except just below the cornea of each side where there is a much greater deposition of the pigment and, in addition, a wedge shaped, brownish, green-blue area about 2 x 1 cm. (These masses were not present during life, but noticed a few minutes after death.) Eyes: The right pupil is slightly larger than the left which is of about average size; both eyeballs sunken. The ears are small. The auricular cartilages through the skin appear leaden gray. There is a small nodule on the upper margin of the left ear, grape seed in size, shows grayish-pink pigmentation in the deeper portion. The external genitalia show no abnormalities, except a faint bluish discoloration on the upper surface of the glans.

(The organs removed through abdominal incision).

**HEART:** Somewhat enlarged, weighs 360 gm. There is considerable diminution of fat below the epicardium. The right side of the heart shows no abnormalities, except at the base of one pulmonary valve cusp and at its attachment to the artery in two places there is bluish discoloration of the intima. The left auricle is moderately dilated, the walls not thickened; the endocardium has the usual appearance except at one place above the auriculoventricular ring where there are numerous, small friable vegetations. Mitral valve—the aortic leaflet shows on its upper surface, near the auriculoventricular ring, a number of small friable, grayish vegetations. The other cusp is strikingly altered. There is a large irregular, friable mass along the line of closure and free edge, yellow in color, in part calcified; the vegetation continues down the associated chordae. The left ventricle is moderately dilated, not appreciably thickened. The papillary muscles are stretched, somewhat flattened; the endocardium thin and glistening. Aortic valve: cusps thin and delicate. At the attachment of the cusps to the ventricle and aorta there is extensive bluish black pigmentation of the endothelium over a considerable area. This pigmentation is visible also on the posterior aspect of the aortic leaflet of the mitral valve. The base of the aorta shows numerous slight elevations, due to small.

7. Dr. N. W. Janney has already published a report of the chemistry of this case, *Am. J. M. Sc.* **156**:59, 1918.

soft, yellow, opaque patches in the intima. The coronary vessels are not tortuous. The walls are somewhat thickened and show scattered soft yellow opaque patches in the intima; just beyond the left coronary orifice there are a few patches of bluish pigmentation of the intima. Left myocardium on section pale and flabby. Here and there are gray flecks replacing muscle. There are also gray streaks associated with the vessels. No abnormal pigmentation of myocardium.

**LUNGS:** The right lung weighs 690 gm. It is voluminous. The upper lobe is strikingly cushiony, especially anteriorly. The lobe also feels soggy. The pleura in general is thin and glistening, except at the apex where there are numerous puckered scars to which are attached dense fibrous tags. Below these pleural scars there is an irregular, indurated pigmented mass about the size of a robin's egg. In portions of this scarred area there are small, dry, cheesy and calcified masses. The remainder of the lobe has a watery, dull, pinkish red color, mottled with black; although crepitation is made out the air spaces contain a considerable quantity of thin fluid. Dissection of the branches of the pulmonary artery show a number of soft yellow patches in the intima. The bronchi show nothing abnormal. The hilic lymph glands not appreciably enlarged, show intense black pigmentation.

The left lung weighs 650 gm. It is voluminous. The upper lobe is inelastic, cushiony. The lower lobe feels soggy. Dissection of the vessels shows atheromatous patches in the arteries, similar to those on opposite side. The cartilaginous rings of the larger bronchi appear bluish through the mucosa. On cross section, however, they appear ochre colored. The pleura is thin and glistening everywhere. On section the upper lobe crackles. A mottled pink and black surface presents. The air spaces contain a small amount of thin fluid, especially in the lower portion of the lobe. The lower lobe on section shows a pinkish-red moist surface. Thin fluid exudes in considerable quantity from the air spaces.

**LIVER:** Weighs 1,750 gm.; shows no macroscopic abnormalities.

**SPLEEN:** Weighs 350 gm.; measures  $16 \times 9 \times 4$  cm. About twice average size. It has the average consistency. The capsule is thin. Toward the upper pole there is a triangular area with sides  $2\frac{1}{2}$  cm. and base  $1\frac{3}{4}$  cm., yellow in color, opaque, depressed a few millimeters below the general level. On section of the spleen a striking picture presents. The surface is soft and pasty, red in color. Scattered throughout the pulp are numerous small gray areas about pinhead in size. The pulp scrapes off readily on the knife. The trabeculae are increased in number, but not in size. The depressed area noted on the surface is found to be a part of a typical wedge shaped infarct, homogeneous throughout, dry, yellow and opaque, except at the apex where for a considerable distance the tissue has a decidedly bluish color.

**PANCREAS AND SUPRARENALS:** No appreciable abnormalities.

**KIDNEYS:** The kidneys together weigh 500 gm. Both are apparently alike. Each measures  $12\frac{1}{2} \times 8 \times 6$  cm. Each moderately enlarged. The capsule strips readily, showing a smooth surface in which the veins are prominent. In addition, innumerable pinpoint and larger bluish black spots are seen. On section, a striking picture presents. The cortex is quite uniform in width, averages from 8 to 9 mm., has a watery gray-reddish appearance, streaked and dotted with brownish and bluish pigmentation. The striations are not very distinct but are fairly regular. The glomeruli are inconspicuous. Brownish and bluish pigment streaks and dots are quite extensive in the medulla and most striking in the papillae.

**BLADDER:** The bladder of average size, the walls of average thickness, contains turbid urine. The mucosa is pale except for a few scattered areas of injection, especially marked in the trigone. The prostatic urethra presents a striking picture; there are stony, bluish pigment masses varying in size from



pinpoint to grape seed; in some places entirely covered by mucosa, elsewhere only partially covered. There is no injection about these masses.

**PROSTATE:** The prostate is of average size and consistency. On section it contains a number of bluish black pigment masses varying in size from pinpoint granules, to several as large as peas. The nodules are stony in consistency.

**SEMINAL VESICLES:** The seminal vesicles are thin walled, not pigmented.

**VESSELS:** The aorta is elastic, the walls of average thickness, the circumference in upper thoracic portion 5 cm. There are numerous rather broad longitudinal yellow opaque masses in the intima throughout the length of the aorta. Just at the commencement of the thoracic portion there is an atherosclerotic plaque which shows considerable bluish black pigmentation over a surface of about a square centimeter. In addition there is a slight diffuse bluish pigmentation of the intima for a distance of 4 cm, in the neighborhood of the intercostal vessels.

**NECK ORGANS:** Only the lower part of the trachea was removed. This shows a pale, thin mucosa through which the cartilaginous rings have a decidedly bluish color. This is true also of the bronchi. On cross section, the pigmentation of the cartilaginous rings is found to be central; in some, it is most marked on the convex portion. The outer rim of pigmentation has a bluish cast; the deeper portions are brown.

**INTESTINES:** There is some apparent hyperplasia of the lymphoid tissue of the small and large intestines. In the colon there are also a number of irregular areas from 1 to 2 cm. square, having a smooth, pearly scarred appearance with thin brown pigmented periphery, suggesting healed ulcers.

**SPINE:** The bodies of the lumbar vertebrae are considerably flattened, the intervertebral discs are narrower than normal and almost bony in consistency; the striking change of the discs is the diffuse, intense bluish black pigmentation. The anterior ligament of the spine macroscopically shows no pigmentation.

**THORAX:** The lower portion of the sternum and adjoining costal cartilages and ribs were removed through the abdominal incision. The costal cartilages present a striking picture; they are hard and everywhere show an intense bluish black pigmentation. The removed ribs and portions of sternum, however, show no apparent pigmentation.

Owing to the fact that permission was granted for a partial necropsy only, the larger joints of the body could not be investigated.

Roentgenograms of all the joints were made, however, and showed changes characteristic of arthritis deformans of the spine with well marked changes of the larger joint (hip and knee) especially about the attachments of the capsules. The smaller joints showed very little change. (Dr. Th. Scholz).

**Histologic Report.**—**TRACHEAL CARTILAGES:** Sections show diffuse pigmentation of the matrix about the cartilage cells and clumps of fine brown granules in the perichondrium. Most of the pigment is deposited in the matrix and immediately surrounding the cartilage cells.

**COSTAL CARTILAGE:** Section shows diffuse brown pigmentation of the matrix. In addition, a number of degenerated cartilage cells contain diffuse and granular brown pigment. The perichondrium is pigmented in places: the pigment present in the form of small brown granules.

**INTERVERTEBRAL DISC:** Intervertebral disc considerably narrower than average, in part composed of fibro-cartilage, in part there are large cartilaginous like plaques. In the matrix of these latter there is diffuse brown pigmentation. In the fibrous portion near the anterior ligament there is considerable granular brown pigmentation.

**AORTA:** Section shows a few atherosclerotic patches in the intima, associated with which there is a considerable amount of extracellular brown pigment in diffuse and small granular form.

**PROSTATE:** The architecture in general is normal. There are rather numerous corpora amylacea in the glands. These vary in appearance. A few show a large amount of diffuse brown pigment in the central portions, the peripheral portions unpigmented, stained pink (eosin). Various stages of pigmentation are seen, including large and small corpora amylacea, diffusely and homogeneously brown stained. About a few of the glands containing the pigmented corpora, there are accumulations of round cells, principally mononuclears. A number of the glands containing these masses show partial or complete absence of the epithelium.

**ENDOCARDIUM:** This is considerably thickened. To it is attached a large thrombus mass, composed of strands of fibrin, red cells and fragmented leukocytes. Another section shows an area of the thrombus in which there is beginning calcification. In the deeper layers of the endocardium there are small masses of extracellular brown pigment in the form of fine granules. Section stained by Gram-Weigert stain shows in the outer portions of the thrombus numerous small round diplococci, many in small chains.

**KIDNEY:** There is some distortion of the striations. In areas there is an increase in the interstitial connective tissue; in some of these areas there is an accumulation of round cells in considerable number. In a number of these areas and also elsewhere the glomeruli have an altered appearance. The glomerular tuft is adherent to the capsule in one or more places. In places the glomerular sac contains amorphous, pink stained material and a few large mononuclear cells. In a very few glomeruli there are a large number of mononuclear cells within the sac, all filled with fine, brown pigment granules. The neighboring convoluted tubules also show a deposition of a large amount of granular brown pigment in the epithelium. In sections stained with silver nitrate, the ochronotic pigment is found in the form of very fine granules in cells of the proximal convoluted tubules and in the form of larger granules in the intact and desquamated cells of many of the ascending limbs of the loops of Henle and the various collecting tubules. The cells of the distal convoluted tubules contain the granular pigment in moderate amount. In general the pigment in the lumina of the tubules is diffuse. In places, however, desquamated cells containing granular pigment are present. In addition to these changes, a number of the tubules contain nucleated cells mostly polymorphonuclear leukocytes and in places the interstitial tissue shows accumulations of similar cells. In addition, in the interstitial tissue of cortex and medulla there are scattered large mononuclear cells containing brown pigment.

**SPLEEN:** Section shows a very large, triangular area of homogeneously pink stained amorphous material in which phantoms of former splenic structures are seen. In addition to the pink stained material there is, in places, some nuclear dust and more strikingly there are clumps of intra and extra cellular brown pigment. The greatest deposits of the pigment are found immediately surrounding this infarct, in the new formed connective tissue, which is present as a fairly wide band; the remainder of the section shows normal looking trabeculae and vessels. The malpighian bodies are very small, and lessened in number. There is, however, an increase in the nucleated cells of the pulp. There are numerous plugs of cocci in the splenic capillaries. Another section of the spleen shows the presence of a number of clumps of yellowish brown pigment scattered throughout the infarct. In the center of this infarct there is the remains of a large blood vessel plugged with homogeneous, pink stained material.

**LIVER:** This shows considerable engorgement of the blood vessels in the central portions of the lobules. There is a striking increase in the number of nucleated cells in the capillaries. In one capillary a very large clump of cocci is seen.

*Microchemical Report.*—In sections stained by Nishimura's method, the ochronotic pigment, diffuse and granular, does not show the reaction for iron.

In formalin-fixed material, the diffuse ochronotic pigment is stained orange red by neutral red (1 per cent. aqueous solution, three hours at 56 C.); the granular ochronotic pigment, however, is not stained by this method.

The granular ochronotic pigment behaves microchemically very much like the pigment of brown atrophy. Both are decolorized by (1) potassium permanganate, sodium sulphite, oxalic acid. (Potassium permanganate, 1/4 per cent. solution, one half hour; equal parts of oxalic acid and sodium sulphite, 1 per cent. solution, 10 minutes.); (2) surgical solution of chlorinated soda (from 15 to 30 minutes), and (3) bichromate sulphuric acid solution (potassium bichromate, 10 gm.; sulphuric acid concentrated, 12 c.c.; water, 100 c.c.) one half hour. Both the diffuse and the granular ochronotic pigment are stained brownish black by silver nitrate (fresh 2 per cent. solution silver nitrate, twenty-four hours at 56 C.). The form and distribution of the pigment are best demonstrated by this method.

#### SUMMARY OF FORTY-FIRST CASE

*Clinical.*—The diagnosis of ochronosis was made in this case because of the bluish discoloration of the cartilages of the ears and skin of the axillae; the pigmentation of the sclerae and the excretion of a dark urine becoming black on standing. In addition the patient had a deforming arthritis of the spine and larger joints and a mitral endocarditis: complications frequently present in ochronosis.

*Chemical.*—Examination of the urine was repeatedly negative for alkapton body. The pigment obtained from the urine, from a costal cartilage and that from the prostate of the case gave the reactions for melanin. The pigment from these three sources had similar characteristics. The chemical findings are in accord with the belief that ochronosis is dependent on a disordered metabolism of phenol derivatives.

*Pathologic.*—As in the cases previously reported, the cartilages (costal, tracheal, bronchial, auricular and xiphoid), and fibrocartilages (intervertebral discs) are deeply pigmented (bluish black). Large stony masses of bluish pigmentation are found in the prostate and prostatic urethra. The kidneys likewise show extensive pigmentation. The endocardium, intima of the aorta and coronary arteries, skin and sclerae are less intensely pigmented. The pigment is not deposited in any quantity in intact intima and endocardium but in areas of degeneration in these structures, however, macroscopic deposits occur. Diffuse ochronotic pigment is present in albuminous masses (renal casts) and concretions (corpora amylacea of prostate). Fine pigment granules are present in the epithelium of proximal convoluted tubules, and coarser granules are present in the cells of the ascending loops of Henle, distal convoluted tubules and the collecting tubules.

The pigment is predominatingly diffuse in the matrix of the cartilage and fibrocartilage and when associated with albuminous masses and concretions. It is predominatingly granular in perichondrium, periosteum, tendons, fascias, connective tissue and in certain

renal cells. It is present in diffuse and granular forms in injured and degenerated areas.

The histologic picture in the kidney sections suggests excretion of the pigment by the cells of the proximal convoluted tubules. The picture likewise suggests a partial reabsorption of the fine pigment by the cells of the loops of Henle, distal convoluted tubules and collecting tubules, and a transformation of the pigment into a more granular form. The form and distribution of the pigment is demonstrated best in histologic sections stained with silver nitrate.<sup>8</sup>

We are indebted to Mrs. H. G. Friedman for her kind assistance in preparing this paper.

8. Other references bearing on this subject are: Poulsen: Literature to 1910, Beitr. z. path. Anat. u. z. allg. Path. **48**:346, 1910; Literature to 1912, Münch. med. Wchnschr. **59**:364, 1912; Beddard and Plumtree: Quart. J. M. **12**:505, 1911; Umber and Bürger: Deutsche. med. Wchnschr. **48**:2337, 1913; Jantke: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:617, 1913; Heymann-Giessen: 1913; Vogelius: Hospital tidende. 1164, 1914; Sprunt: Ochronosis, Nelson's Living Medicine **3**:211, 1920; Howard: Ochronosis, Oxford Medicine **4**:223, 1921.

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A NOTE ON THE RELATION OF THE AXILLARY  
ARTERY TO THE BRACHIAL PLEXUS

## A NOTE ON THE RELATION OF THE AXILLARY ARTERY TO THE BRACHIAL PLEXUS

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NEW YORK

A. *Introduction.*—The brachial plexus is not a very simple structure. However, the use of a bit of anatomical information may serve to make its complicated branching very much easier to remember.

*The division into dorsal and ventral branches.*—The first fact of importance is that it is composed of branches which may be divided into ventral and dorsal groups. These ventral and dorsal branches arise in the ventral branches of spinal nerves. If, for the sake of simplicity only the five main branches which go to the muscles and skin of the arm, forearm, hand and fingers are considered, we find that these may be divided into two general groups, the circumflex and musculospiral on one hand, the musculocutaneous, median and ulnar on the other. If we represent these two groups separately we get pictures which are shown in Figures 1 and 2.\*

B. *The part played by the axillary artery.*—Figure 3 shows a more complicated interlacing. This is readily understood, however, by the second anatomical fact which is the one to be emphasized. The axillary artery is at the bottom of the complexity. If we assume that the axillary artery were differently placed than it is, that it did not pass between the two heads which make up the median nerve (Fig. 3) it will be seen that the ventral nerve of the arm, forearm, hand and fingers, that is, the combined outer and inner cord, would be fused and as simply constituted as the dorsal nerve, the posterior cord. The direction of fusion of nerves is always towards the axis of the central nervous system, just as the direction of branching is always away from it. It is quite obvious therefore, that the presence of the axillary artery accounts for the lack of fusion and hence the complexity. The musculocutaneous, median and

\* NOTE.—The reader will find the following an excellent article on the normal and abnormal structure of the brachial plexus: "The Brachial Plexus of Nerves in Man—the Variations in Its Formation and Branches." Abram T. Kerr. The American Jr. of Anatomy, Vol. 23, No. 2, March 15, 1918, pp. 285-395.

ulnar nerves are but branches of the ventral nerve dignified by special names. The circumflex and musculospiral nerves are but

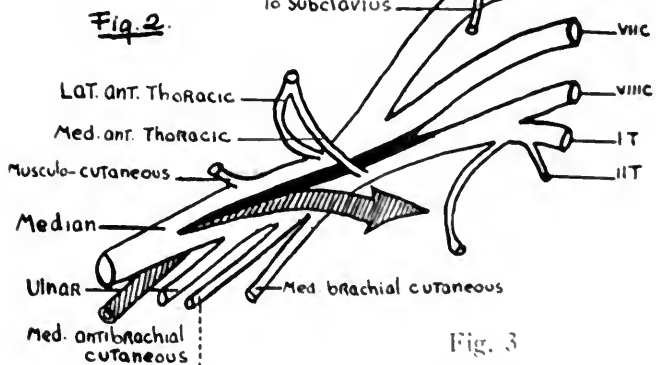
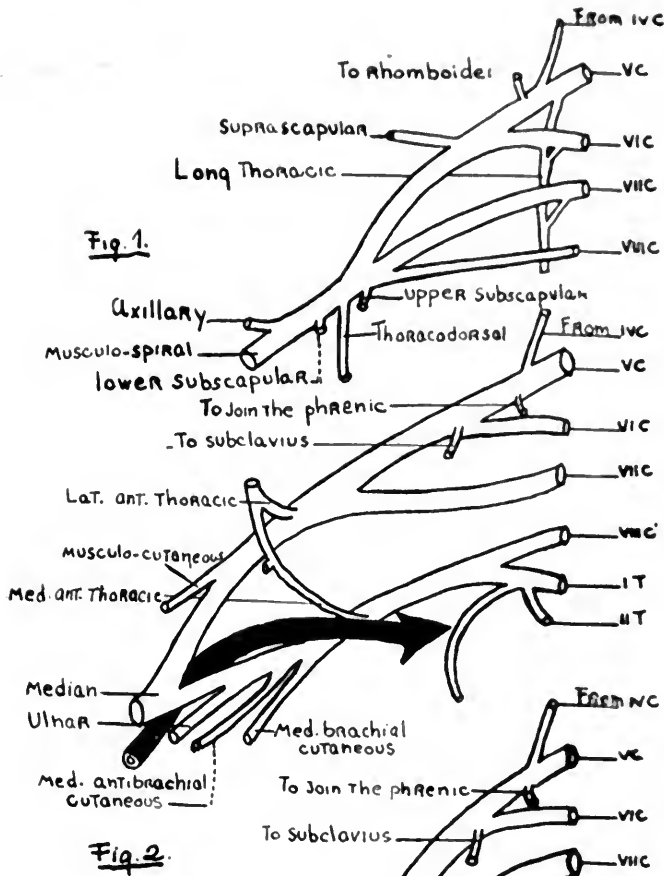


Fig. 3

branches of the dorsal nerve also dignified by separate names. The reason that these branches occur is largely due to the necessity of

supplying *topographically distant* structures, that is, the muscles of the shoulder on one hand and the muscles of the arm and forearm on the other.

KEY TO DIAGRAM (p. 323)

Figure 1 represents the dorsal trunks and branches of the brachial plexus. The fusion into a single branch, the posterior cord, is shown.

Figure 2 represents the ventral trunks and branches of the brachial plexus. The axillary artery is represented by the black arrow. The way in which it prevents fusion of the two heads of the median is illustrated by the course of the artery.

Figure 3 is schematic and shows what would happen if the axillary artery were absent. The black area between the upper and lower cords indicates their fusion, which would occur if the artery were not present. These two cords would then form a single ventral cord like the dorsal or posterior cord illustrated in figure 1.

The diagram illustrates the principle that the direction of fusion of nerves is always towards the axis of the central nervous system while the direction of branching is always away from it. These two activities are constantly at work. As a result, extremely complex internal nerve plexuses are produced.

The position of the axillary artery represents one of the many anatomical deterrents of fusion centralward of peripheral nerves.



# BRADYKINETIC ANALYSIS OF SOMATIC MOTOR DISTURBANCES IN NERVOUS DISEASES

ANALYSIS OF MOTOR DISORDERS BY THE AID OF  
ULTRA-RAPID MOVING PICTURES

BY

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# BRADYKINETIC ANALYSIS OF SOMATIC MOTOR DISTURBANCES IN NERVOUS DISEASES

## ANALYSIS OF MOTOR DISORDERS BY THE AID OF ULTRA-RAPID MOVING PICTURES

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The subject of disturbed motor function has been carefully studied for many years with some interesting results especially in the clinical field. Motor defects, however, have proved elusive to exact interpretation and in many respects knowledge in this particular field is still in need of assiduous cultivation. It seems probable that the principal difficulty lies in the present imperfect understanding of vertebrate motion as a whole, and in this light the interpretation of disorders in the complex motor mechanisms of man appears all the more perplexing. It has been apparent to the authors and others interested in this important topic that only by a combination of many different methods may the problems involved in the motor disturbances be solved. The object of this paper, therefore, is to present certain newer methods of study which may be applied to these disorders, and at the same time to demonstrate the results derived by an application of the methods to certain well-defined groups of motor disorganization.

Weisenburg, a few years ago, demonstrated the value of cinematographic reproduction in the study of nervous diseases. In the present investigation more recent developments in photography with the high speed camera are introduced in the analysis of deformities in motion.

In an attempt to analyze and record the

disturbances of motility, one is impressed at the outset by the inadequacy of the nomenclature employed in describing various types of abnormal motion. Most of the terms in common use not only fail to be descriptive, but lexicologically many of them are non-descriptors. For the present and until adequate replacements in terminology may be made, it seems desirable to adhere to the accepted nomenclature.

### METHOD AND MATERIAL

Ultra-rapid moving pictures of patients by means of the "Novograph" camera were taken at the rate either of one hundred and sixty or three hundred exposures per second. The ordinary cinematographic rate is sixteen exposures per second, so that the ultra-rapid rate is from ten to eighteen times as fast. The normal rate of projection on the screen offers opportunity for the study of every component in each movement. The motion, thus slowed down, serves as the basis for what we have called *bradykinetic analysis*.

In studying each of these types photographs were made simultaneously at the usual and also at the ultra-rapid rate of exposure. The screen reproduction of these pictures first shows the subjects photographed at the regular cinematographic rate, followed by the pictures taken at the ultra-

rapid rate, both sets of photographs being reproduced at the usual cinematographic rate of sixteen pictures per second.

The material upon which these studies were made consisted of patients selected from the neurological wards of the Montefiore Hospital for Chronic Diseases. In this selection special attention was given to securing patients showing marked motor disorders the general characters of which have been the subject of much debate and have also occasioned not a little discussion in classification and nomenclature. The motor disorders submitted to bradykinetic analysis include choreiform movements, torsion spasms, extreme intention tremors and cerebellar ataxia. These motor defects occurred in cases of *chronic degenerative chorea*, *astasia abasia*, *dystonia musculorum deformans*, *multiple sclerosis* and *congenital cerebellar aplasia*.

In all the cases studied the motor defect was characterized by some pronounced abnormal and adventitious element of motion which produced a definite deformity of movement. Such adventitious motor elements we have endeavored to describe as objectively as possible in the following enumeration of them:

1. Regular and rhythmical oscillations of parts of the body during muscular inactivity or in volitional action.
2. Irregular arrhythmical oscillations of parts of the body during volitional motion.
3. Sudden isolated twitches of the muscles producing involuntary movements or deflecting the course of volitional motion.
4. Sudden successive twitches of muscles producing involuntary movements or deflecting the course of volitional motion.
5. Sustained mobile spasms of muscles during volitional motion producing rhythmical distortions of the limb, trunk or limited parts of the body during activity of the particular part.
6. Sustained tonic spasms of limited groups of muscles during volitional motion which retard or deform the resulting movements.
7. Sustained tonic spasm in a large num-

ber of muscle groups during activity or in rest, producing distortion of the body together with marked deformity of motion during action.

#### I. ANALYSIS OF A CASE OF CHRONIC DEGENERATIVE CHOREA

This patient was a married woman, thirty-six years of age, born in Russia. She was the mother of five healthy children. Her present illness began when she was thirty-one years old during the fifth month of a pregnancy. Without apparent cause there developed irregular, purposeless, involuntary movements in all segments of the body. A gradual change in conduct was also observed which apparently affected the faculties of attention and concentration. She showed lack of interest in her family and in affairs generally, with a progressive mental deterioration.

The cinematographic study of the patient at the normal rate of projection showed a variety of meaningless and purposeless deformities of motion such as facial grimacing, continuous movement of the eyeballs together with sudden twittings in the trunk, limbs and head. These movements were somewhat too rapid for the typical Huntington's chorea. There was incessant jaw motion as in grinding the teeth, and the tongue and lips smacked at irregular intervals. The abdominal muscles were in almost constant play.

By ultra-rapid photography, the projection revealed striking differences for interpretation. The component elements of the deformities of motion were clearly discernible, and what appeared to be twitching, purposeless movements were seen to have definite associative significance. They comprised a series of symbolic attitudes indicative of emotion. The photographic analysis reduced the speed of movement and resolved the motions of the trunk and extremities into segmental components. These movements now appeared as those of approach and retreat, expressing the appeal of entreaty or negative self-feeling of shame. They clearly represented an emotional flux recognized as

a functional element in some patients with this type of chorea.

The posing and attitudinizing, so impressive in other well-recognized organic diseases, suggest a close anatomical relation of these symbolic movements to the basal ganglia of the forebrain. The thalamus and the corpus striatum which are functionally associated with sensorimotor complexes serve as the centers especially controlling automatic associated acts and attitudes expressing the fundamental emotions. In this light it seems fair to presume that such attitudes as express emotional states in true hysteria may have their subconscious controlling level in these basal ganglia.

Another interesting feature in the bradykinetic analysis was the extreme hyperextension of the left leg at the knee as the patient walked. In this patient the attitude of the limb appeared to be the result of kinetic overflow within the extensors, the check of the antagonistic flexors being defective. The extreme slowness of the antagonistic check response together with a singular wave reaction seen in the extensors suggested a possible failure of elements constituting the so-called static mechanism. A similar failure in stabilizing the kinetic flow is seen in the study of the dystonias, and the imbalance in the synergic units points to a defect in the synergizing influence of the cerebellar reflex circuit.

In summary, the analysis of this case of degenerative chorea discloses a combined defect, in part affecting the kinetic mechanism controlling automatic associated movements and attitudes expressive of the emotions, in part due to impairment in the static mechanism maintaining posture. (Fig 1.)

## II. ANALYSIS OF A CASE OF CHRONIC DEGENERATIVE CHOREA WITH SOME ELEMENTS SUGGESTIVE OF DYSTONIA

The patient was thirty-six years of age. About two years previous he became "extremely nervous" and developed slight twitching in the lower extremities, soon accompanied by a staggering and uncertain

gait. Four months later the upper limbs participated in motor restlessness, consisting of involuntary "flinging" about of the arms followed by shrugging movements of the shoulders. The same disturbance involved muscles of the head and neck. A corkscrew-like motion, chiefly of the trunk, completed the motor disorder.

When admitted to the Montefiore Hospital he had the attitude, movements and gait of Huntington's chorea.

By bradykinetic analysis the attitudinizing and symbolization, so evident in the first case, were apparently distinctly those of hurling or lifting and were too definite in pose and in poise to be a mere chance overflow of kinetic energy into purely accidental designs. Unquestionably there was an element of purpose in these attitudes. The postures were those of aggression and attack, thus expressing what may be expected of the more positive character of the male emotive mechanism. An extensor elevation of the foot (not seen in the accompanying photographic illustrations) as the patient stepped forward, and also a corkscrew-like movement of the trunk upon the pelvis, appeared to be distinctly dystonic elements and suggested a relationship between the dystonias and this type of chorea.

In all the cases presenting clinical features that seem to involve the posturing and attitudinizing mechanism, the motor elements which determine posture seem to be disorganized. In cases of this type the agonist and antagonist are apparently not harmoniously cooperative. This becomes manifest as the several muscles are studied in their slow interplay. Comparison by means of bradykinetic analysis readily demonstrates a marked difference between disturbances due strictly to cerebellar disintegration of the synergic unit, and those forms of striatal disintegration whose pathological anatomy probably lies in the corpus striatum and its immediate basal connections, especially with the red nucleus.

As many observers have pointed out, there is doubtless an intimate anatomical pathological relationship between the various

deformities of motion of the striatal type, and in all of our cases a study of the muscle-group activities brings clinical confirmation of this fact.

The prolonged pronation spasms in this patient and the marked overaction of the extensor muscles holding the raised foot upon the toes, clearly belonged to the group of sustained mobile spasms producing rhythmical distortions of the limbs and body during motion. This phenomenon is particularly prominent in the dystonias.

The tendency of trunk distortion was disclosed as a sudden unilateral pull of flexor trunk groups. The torsion in this case involved rather the upper trunk segment in contrast to that seen in dystonia. There was a suggestion, too, of tic element in the choreic movements which involved especially the axio-appendicular groups of the upper extremities. Analysis certainly demonstrates a variety of elements common to many entities. (Figs. 2 and 3.)

In summary, the analysis of this case of degenerative chorea discloses the fact that sudden isolated twitches of the muscles producing involuntary movements or deflecting the course of volitional motion are to be associated with disturbance in the striatal and cerebellar mechanisms, and that the attitudinizing, although different from that observed in the woman suffering from the same disease, is basically similar in being expressive of primitive emotions. In the case of the male these emotions have a positive self-feeling tone representative of aggression and attack in contrast to the female where these emotions have their expression as negative self-feeling tone in reactions of appeal and retreat. The sustained tonic spasms producing distortions are manifestations of hyperkinetic innervation of muscles recognized as the essential part of the syndrome in those motor disorders known as the dystonias.

### III. ANALYSIS OF A CASE OF MULTIPLE SCLEROSIS WITH ASYNERGIC MOVEMENTS

The patient, a watchmaker, forty-eight years of age, first noticed, when he was

thirty-two years old, a slight and occasional defect in vision, with numbness in his fingers which occurred from time to time. A year later he began to be troubled with a tremor in his right hand especially when executing the more delicate manipulations of his trade. This tremor gradually spread until it involved his entire body. He soon developed difficulty in walking, and in the course of three years his locomotion was so much compromised by a spastic paraplegia that he was forced to give up his occupation. It was about this time that the nature of his malady was recognized.

The study of this case at normal photographic speed discloses many confusing movements as the subject attempts the "finger-to-finger" approximation test. He illustrates particularly well a phenomenon which, in part, characterizes the motor disturbances of disseminated sclerosis, the so-called *intention tremor*. These abnormal movements during voluntary effort were, from an early period in the history of his disease, very extensive, and comprised, indeed, the only symptom present for some time. Original observers of the case placed it among functional disorders.

The analytic projection shows a disintegration of the synergic units throughout the body. Agonist and antagonist are not coordinated. The extensor check fails to hold the flexors and the reverse is also true.

This disorganization is especially obvious in the finger-to-finger test as the point of destination and finer approximation is approached. In slow motion the disproportion in flexion, extension and supination is clearly seen. The arms shoot far beyond the point desired (the analytic photography greatly reducing the speed), they are overextended and again overflexed. The obtrusive feature is a motor disorganization showing dissociation of muscular harmony and asynergia between dominant and check groups of muscles. As has been shown by Weisenburg and Tilney, this type of motor phenomenon is indicative of cerebellar disturbance. The groups of muscles of the trunk and extremities are also involved. The case is one of

integrative asynergia. It would seem then that the "tremor" of multiple sclerosis is of cerebellar origin, that a case such as the one studied must involve extensive cerebellar areas. (Fig. 4.) An even more definite conception of cerebellar asynergia is acquired by a study of a case of cerebellar agenesis.

In summary, the analysis of this case of multiple sclerosis reveals the fact that the so-called intention tremor is a static defect due to the dissociation of the synergic units of the body consequent upon disproportionate innervation of the dominant and check elements in the muscle groups.

#### IV. ANALYSIS OF A CASE OF ASTASIA ABASIA WITH EXCESSIVE ISOLATED AND SUCCESSIVE SPASMS

The patient was a young girl, seventeen years old, apparently with nothing in her family history to cause the onset of a profound psychoneurosis. The abnormal movements consisting of isolated and successive muscular spasms had their exciting cause some four years previous in the fear of a thunder storm. Associated with these movements was a psychic attitude of dread with sudden increase of the motor agitation and facial expression of anxiety upon any sudden noise. Up to that time there had been no disturbance of consciousness nor had there been objective or subjective sensory symptoms of hysterical nature.

The motor manifestations were those of astasia abasia, the patient being unable to stand or walk without support.

At normal speed photography, as the patient stood and walked with support, the gait was not suggestive of any organic nervous disease. The segments of the body, as the muscles moved the joints, acted in harmony and unison; there was no disintegration of the synergic units. The lower extremities in walking performed a series of short steppage movements, and in standing these continued in rapid succession. Analyzed under increased photographic speed, rhythmic, well poised, fully coordinated, normally synergic phases of voluntary move-

ment followed in regular order. Their contrast with the preceding studies of organic deformities of motion leaves no doubt of the different character of each. These movements clearly bespeak an intense self-consciousness with acute apprehension of impending danger. They are more complex and studied than the more direct instinctive reactions to fear. Their elaborate character is in marked contrast to the simpler attitudinizing in chorea.

Another muscular phenomenon was observed in this case, namely, a vermicular muscle wave. This was not the result of any artificial or mechanical effect and must have depended upon some inherent quality of the muscle groups. The muscle bellies themselves were apparently the seat of gross morphological changes. Whether this phenomenon is pathognomonic of functional motor disturbances can be determined only upon bradykinetic studies in many other cases. Mr. C. P. Watson, President of the Novograph Company, whose experience with screen photography is vast, and who had witnessed film productions of many athletes and others under varying conditions of muscular activity, had not previously observed this vermicular wave. In the normal projection of this girl there was no suggestion of this wave, but in slow motion analysis the wave was immediately recognized passing slowly from below upward through all the muscles of the right lower extremity from ankle to hip. This appearance resembles the successive surface movements when a strong wind sweeps a field of wheat. It would be of interest to study by bradykinetic analysis a number of functional disturbances in which the somatic musculature is involved. Possibly this wave as demonstrated in this patient is a condition found only in what we are wont to call non-organic or functional disorders.

Note: Some few weeks after the photographic presentation and following a fright, the patient suddenly passed into a kind of hypnotic sleep from which she could not be aroused even by the strongest stimuli, includ-

ing faradic current of great intensity. In the beginning of this state the girl screamed continuously, had tonic and choreic convulsive seizures and assumed bizarre, emotional attitudes. She would constantly repeat, "I am afraid," but could not be aroused to any form of conscious response. There was corneal as well as general anesthesia. The condition continued for some three or four days. She was regularly tube-fed and catheterized. The irregular convulsive seizures were really a marked intensification of previous movements with an intense psychic phase added; they were so violent as to yield only to chloroform narcosis pushed beyond the primary stage. The patient at no time showed signs of exhaustion. There were several periods of these seizures, each lasting a few days. It seems to be of some significance that the patient was restored to consciousness by the playing of phonograph records. A more careful study of the intricate psychic associations was not made. The patient has since markedly improved psychically, but it is of interest to note that the toes in which intense flexor movements were observed on the screen have since assumed a definite and fixed attitude in the flexor position, though in sleep they at times become relaxed. (Fig. 5.)

In summary, the analysis of this case of atasia abasia reveals the fact that the irregular, sudden twitchings of the muscles which disturbed locomotion were in reality highly complex and expressive of acutely conscious and psychically much magnified fear. These movements are in marked contrast to the simpler attitudinizing of chorea. The wavelike contraction in the muscles of the leg requires further study before a complete analysis of it may be offered.

#### V. ANALYSIS OF THREE FAMILIAL CASES OF DYSTONIA MUSCULORUM DEFORMANS (A BROTHER AND TWO SISTERS)

We are indebted to Dr. I. Abrahamson for the opportunity of studying this series of cases.

In this family group of dystonia musculorum deformans, each member presented a

different degree of severity and progress of the disease. The family stock was recorded as having been substantially without taint except in one important particular: On the paternal side there was a more or less direct history of dystonia, in that the patients' father's sister and her daughter were afflicted with a disease similar to that of the three patients here described.

1. *The Brother. Incipient Stage. Movements Largely Confined to One Extremity.* The boy was the least afflicted of the group. As in the case of the sisters, his early life up to the time of onset of the present illness was quite normal. The motor disturbance began in his thirteenth year, and as in the case of the younger sister, manifested itself especially in an attempt at execution of finer movements with the right hand, such as writing. The patient was intelligent and had made from the first every effort to overcome his difficulty. He fully realized the progress and serious deformity which the disease had shown in his sisters and was fearful, even before the onset of his illness, that he too might become a sufferer. Indeed, the boy made unusual efforts by exercise and intense mental endeavor to maintain control over the afflicted upper extremities; this he continued with great determination as he felt the right leg, more particularly the right foot, assume spasmodic, uncontrollable, involuntary attitudes in attempting movement.

The cinematographic representation of his gait showed a turning-out of the foot and the sudden flexion at the knee and hip with inward rotation at the hip. In normal projection as he ran, a limp alone was seen. The slow motion for bradykinetic analysis showed a partial failure of coordinate time reaction in groups of agonists and antagonists. A study of our series of dystonias shows this failure as a feature in them all. For example, the forceful hyperextension of the foot, common to all of the cases of dystonia, appears as a failure in the time limitation of the muscular contraction, or, in other words, an excessive overflow of innervation. The peculiar character of this kinetic overflow in the agonist groups differentiates



the organic from the functional disease with which this latter spasmodic condition has often been confused. From the standpoint of muscular dynamics, this excessive muscular contraction is wasteful and unnecessary for the purposes served by the muscle action. A small percentage of energy is expended in the purpose and a large amount in producing useless tonic spasms of the muscles involved.

The slight rotation of the thigh seen on normal projection, together with a slight raising of the foot in equinus position and flexion at the knee and hip, was in reality a widespread disorganization of the movements of the gait. Analysis showed at once that this form of deformity was due to excessive overflow of kinetic innervation.

Any movement designed to serve some definite purpose, as for example, moving the leg forward in walking, may be considered as a transition from an *initial posture to terminal posture*. The leg may be arrested at any intermediate point and be made to assume an *intermediate posture*. The motion, therefore, from the initial to the terminal posture may be regarded as a series of potential intermediate postures between the two limits mentioned (initial and terminal posture). The innervation producing motion through a series of postures from the initial to the terminal is *kinetic*, while the innervation controlling the entire series of postures, both actual and potential, is *static*. In this light two streams of innervation flow concurrently and in harmony through the production of any purposive motion, the kinetic stream producing movement, and the static stream maintaining actual and potential posture. One or both of these currents may be subject to excessive innervation and produce excessive muscular activity in motion or in posture. Bradykinetic analysis indicates that both types of innervation are excessive in the dystonias with resultant extreme degree of movement and extreme postures amounting in many instances to actual distortions. In effect, therefore, dystonia is due to hyperkinetic and hyperstatic innervation. This is seen in this patient whose trunk tended to a rotary action about the pelvis while he was

suddenly raised upon the toes of the right foot and thrown, as it were, as from a springboard. The extreme pronation of the upper right extremity gave the characteristic pose which in the more advanced stages assumes fixation. The torsion of the pelvis, commonly described in this disease, was only suggested in this patient, though a study in slow motion of the long muscles of the back and those about the pelvis showed the tendency to rotary motion.

In the study of the individual muscle groups by bradykinetic analysis, those of the right thigh stood out with abnormal intensity during periods which demanded their function only to a slight degree, thus indicating the hyperkinetic innervation. This appeared as a prolongation of muscular action. To a less degree this was conspicuous in the left thigh. It has been suggested that this latter may be an incipient phase of the characteristic deformities in the dystonias. The patient made every effort to overcome the deformity of movement, and in the early stages of this disease there seems to be no question that volition exercises some beneficial influence. Indeed, in a case seen in its incipient stages by one of us (Goodhart) and shown at the New York Neurological Society, exercises, relaxation and re-education added their measure of influence in causing the deformities to disappear entirely. The patient occasionally, and only when extremely tired, shows a momentary dystonic spasm. In the advanced stages, however, voluntary effort at control intensifies the deformities of motion. (Fig. 6.)

2. *One Sister. Dystonia Movements More Extensive and Intense.* The patient, an intelligent girl of eighteen, was the second in this family of three to become a victim of dystonia. Her condition represented a degree of involvement between that of the slightly affected brother and the more advanced case of another sister. There was no retardation in early development, the three children of this family having begun to walk and talk before the age of two.

When twelve years old the patient noticed a sudden jerking or forced movement in the

form of pronation, beginning in the right hand. This motor difficulty showed definite advance in the performance of skilled movements generally, particularly in writing, and there were peculiar stiffening and worm-like movements in the fingers which seemed to extend suddenly upon attempts to grasp objects. The left hand soon became similarly affected. Within a few months the right leg showed some disturbance of motility. Gradually a feeling of tension developed in the leg, the extremity became flexed and the hip more or less fixed in this position (Fig. 7). As in all of these cases of dystonia musculorum deformans, this patient became easily exhausted upon attempts at voluntary movements. This is doubtless due in large measure to the efforts at suppression and the extra endeavor to use muscle groups, some of which are already involved. The relation of the trunk and pelvis was such as to cause lordosis of the lower dorsal and lumbar spines, and the entire body assumed an attitude of emprostotonos. The characteristic hyperextension of the foot was present and a limp much more pronounced than in the brother. There was a marked likeness in the poise and position of the three members of this group. The appearance of all of them warranted Oppenheim's synonym for the condition—*Dysbasia Lordotica Progressiva*.

It is apparent that changes in the static mechanism caused definite alterations in the muscle groups, especially in the hamstrings. Fixation developed at the knee and the hip. The hyperstatic condition was also seen in the inward rotation of the knee as well as in the marked plantar flexion of the foot and the toes. When studied by means of slow motion pictures the hyperkinetic overflow became evident in the soleus gastrocnemius groups. Fixation at the hip restricted the extension so that the trunk was not projected to the usual degree and in the characteristic manner. (Fig. 7.)

3. *Second Sister. Condition More Advanced. Dystonic Movements More Extensive.* The third case of the series was the most advanced of the three children in this family. The patient was a young woman

twenty years of age. Her condition was the result of seven years of progressive development. The manifestations began in the lower extremities and gradually extended to the upper extremities. The case is, perhaps, unique, in that it refutes the claim of most observers that the muscles supplied by cranial nerves are not involved in the disease. The facial muscles and those of the tongue were affected to such a degree as to make the patient's speech difficult and almost unintelligible. The speech was of a drawling character, articulation being finally accomplished after efforts to overcome a pronounced hypertension, evidently caused by a hyperkinetic overflow. The extreme muscular activity seemed to be due to sustained tonic spasms in a large number of muscle groups many of which were not pertinent to the particular motor act in process. These spasms produced distortions of the body with marked deformity of motion.

At the usual cinematographic rate of reproduction the patient bore a strong resemblance in her gait, attitude and posture to the brother and sister. There was a similar flexor fixation at the knees, with an equinus fixation of the feet when the patient stood. In locomotion the right heel failed to reach the floor. The typical pronation position of the forearms was emphasized.

In slow motion pictures the analysis discloses the typical hyperkinetic and hyperstatic disturbances. The marked overflow of innervation is apparent in nearly every group of muscles in the body, producing needless and often untimely postures as well as unnecessarily active motions and movements wholly unnecessary to the acts performed. (Fig. 8.)

#### VI. ANALYSIS OF A CASE OF DYSTONIA MUSCULORUM DEFORMANS SHOWING EXTREME SUSTAINED SPASMS

The patient was a young man, twenty-five years of age, born in Switzerland. His family and personal histories were unimportant medically. The first indication of his malady appeared during his twelfth year when the

muscles of the right leg began to act peculiarly, stiffened up and produced an awkward gait. In locomotion, as the condition advanced, the whole body would be brought forward with a "pitch or lurch" to the right.

An important feature in the history of this case was the fact that, following a long period of rest and relaxation treatment, there was pronounced improvement in the dystonia, and for several years there was almost complete cessation of abnormal movements. During this period, under conditions of intense emotion only would there be mild recurrences. From his seventeenth year, however, after an experience causing intense mental strain, there occurred a rapid generalized involvement of the somatic musculature, reaching a remarkable degree of distortion.

At the normal rate of cinematographic reproduction he appeared as a trained athlete, his muscle groups standing out prominently in their unusual development. The hypertrophy was real and the muscle strength in proportion. Testing the muscle capacity by feats of strength it was easy to determine that good muscle power was present, but the lack of proper control made it impossible for him to direct his energies to accomplish any purpose. In endeavoring to wrestle, the patient's opponent felt the full power of the groups of muscles, but the static dissociation threw the patient into involuntary attitudes which defeated his efforts and thwarted his skill. The kinetic energy appeared to develop good muscular power, but produced sustained spasms which caused perversions in all of the motor performances which he undertook. The trunk muscles were quite as much involved as those of the extremities. They threw the body forward and were augmented in their unchecked force by the upward projection of the extensors of the thigh, leg and foot. The force in extension movements was so great as literally to hurl the patient's body forward. In the previous cases attention has been called to the typical equinus tendency which forced the patient to walk upon the ball of the foot. The sudden and uncontrolled flexor and torsion spasms

of the trunk with the extension of the arm, gave the impression that a heavy object was about to be hurled with great force. The incessant and powerful muscle activity with its violent contortion suggested a sudden overflow of kinetic energy causing extension of the entire body musculature. Now the flexor groups were in dominant ascending power, and again the extensors. The normally opposed groups seemed to fail in their check function in time to arrest this involuntary overflow.

The details of this extravagant expenditure of energy are revealed in bradykinetic analysis. The characteristic attitudes and poses, clearly showing how the static mechanism gives rise to the clinical pictures, are much more generalized than in any of the previous patients, but the distinguishing features of the muscular deformities are at once recognized. Indeed, if the film is stopped, almost any single picture would enable one to diagnose from its pose the nature of the malady. There is an absence of permanent contractures, conspicuous in some of the other cases, especially those of long duration. This is in part due to the almost universal involvement of the somatic groups, and probably also to the apparent absence of pathological changes in the muscles.

That the emotions exert a strong influence over these bodily movements is generally understood, and this is true of all forms of pyramidal and particularly of extrapyramidal lesions. Sitting in a perfectly quiet environment, the patient had no difficulty in inducing almost complete relaxation, and the abnormal movements ceased. He was able to feed himself and even move about slowly, with almost normal control. Being morbidly sensitive, he felt his isolation to a degree which had a decided effect upon his psyche. The slightest suggestion that he afforded amusement to others intensified his loss of control. A mental attitude developed in this case which tended to bring about an unfortunate state of conflict between his psychic state and his environment. This was not the fact in other cases. It makes necessary a further study of the psychology of the indivi-

dual, especially in relation to motor control. (Figs. 9 and 10.)

VII. ANALYSIS OF A CASE OF DYSTONIA MUSCULORUM DEFORMANS SHOWING THE "DROMEDARY ATTITUDE" AND SO-CALLED SEMILUNAR FOOT

The patient was a girl of seventeen with good personal and family history. The long duration (ten years) and extreme degree of the manifestations peculiar to this disease give the case an especial interest. Born in this country of Russian Jewish parentage, the girl's first seven years of life showed normal development. At about the age of seven, peculiar, involuntary movements appeared, which were at first limited to the right foot but gradually spread to the right hand and arm. The description of these initial motor symptoms given by many of the patients suffering from this type of the disease, furnishes a conception of the character of this muscular involvement. It suggests what is understood under the term spasm.

In the course of the following three years various muscle groups became affected while involvement of the musculature of the back and neck was followed by that of both extremities upon the left side. The extension of the disease to all of the somatic groups covered a period of from three to four years, culminating in the incessant movements characteristic of her condition. The muscles supplied by the cranial nerves, with the exception of the sternocleidomastoids, and the trapezii were not involved. When in the prone position, the patient found lying on the left side most comfortable and the extreme deformities, those that were transient and those that were permanent, were then well demonstrated. The patient's movements, because of contractures and resulting deformities, were extremely slow, so that the contrast between normal and high speed photography is not so striking in this case as in others. The appearance of the patient in the cinematographic reproduction at normal speed was that of the typical *dromedary attitude and locomotion*. The extreme deformities of the feet were unusual, and had it not been for a definite history, we would

have suspected a condition of congenital clubfoot.

In the slow motion pictures the characteristics of dystonia are demonstrated, though the extreme contractures and joint deformities have changed the original attitudes and now limit the play of muscular groups. Even in the normal projection and now more clearly analyzed, the movements and postures appear as overaction of certain groups of muscles, and it can be readily seen why the term dystonia has been adopted. As a matter of fact, the defect is due to hypertonia, inasmuch as the hypotonia is relative and not real. However, lordosis and dysbasia are even more obtrusive symptoms in nearly all cases. There is a fixed flexion at the hip and knee, with inversion and extension of the right foot, while the left foot is extended. The phalanges of the feet are strongly flexed increasing the marked concavity present in the plantar arches, and giving rise to the formation of what is called "semilunar" foot. So extreme are the deformities that the plantar surfaces of the feet do not touch the floor. Closer study brings out flexor-extensor movements of the fingers of the paralysis agitans type. Abnormal involuntary movements in various groups of muscles keep the body, both in the prone and the upright position, in continuous action. The muscular contractions of the various groups are so constant as to keep up a series of sustained, arrhythmical spasms. The muscles of the lower extremities were atrophied while those of the upper extremities and their axio-appendicular groups were greatly hypertrophied. The partial atrophy of the muscles of the legs was doubtless due to local changes in the joints, those of the ankles and feet being ankylosed. These were doubtless secondary mechanical results of the muscular disorganization.

Sudden tic-like movements of muscle groups in the upper extremities appeared, occasioned when the patient was under emotional strain. They appeared to be myoclonic in type. In no single case of dystonia have we seen such a combination of abnormal movements. Indeed, one might hesitate to

designate this case as one of pure dystonia musculorum deformans, although it possessed the distinctive features. (Fig. 11).

#### VIII. ANALYSIS OF A CASE OF DYSTONIA MUSCULORUM DEFORMANS WITH PROGRESSIVE IMPROVEMENT

This patient is one of those cases of dystonia which have shown improvement by means of physical re-education. Bradykinetic analysis reveals certain deformities of motility which our previous studies have shown to be characteristic of the organic affection. The boy was normal until his eleventh year. About a year previous to this he fell from a fire-escape on the first floor of a building. He landed upon his feet and feeling no ill effects whatever, continued playing. There was nothing in the history of the following year to indicate any connection between the fall and the onset of his illness one year later. The first symptom was an outward rotation of the right lower extremity. Some two years later sudden involuntary pronation movements of the right hand, followed about a year later by an involvement of the left lower extremity, completed a picture which gave the patient the characteristic cast of the milder type of dystonia. His appearance on re-examination showed a decided improvement as compared to that of about a year previous. Nevertheless, viewed in the light of the patients already studied, there was characteristic pose and attitude of the body as a whole, and of the extremities in particular.

In the slow moving pictures the right lower extremity showed peculiar external rotation at the hip, knee and ankle, with hyperextension of the foot in sustained equinus position. Bradykinetic analysis of this motor phenomenon was, in itself, sufficient to make the diagnosis. The tendency to pronation position of the left upper extremity; the extreme extension of the toes of both feet at the same moment as the patient was about to turn, the pronounced upward shift of the entire right lower extremity, the lordotic curve with the suggestion of torsion in the trunk, were unmistakable.

The patient was next observed as he

moved "on all fours." This position, as the patient moved forward, brought out even more emphatically the special deformity apparently due to defective postural fixation. Obviously, this deformity of movement would not have been apparent had he moved forward on hands and knees; the defect in attitude just alluded to would not have been brought out, since the extensors of the lower leg and foot would thus not have been brought into play. To demonstrate this fact it was necessary to observe him moving forward resting on fingers and toes and ball of foot. (Figs. 12 and 13.)

In summary, the analysis of these cases of dystonia musculorum deformans reveals the fact that an actual disorganization exists in the relation of the static and kinetic mechanisms. The marked hyperstatic defect appears to produce initial and intermediate postures of such extreme fixity that an unusual amount of kinetic energy is required to overcome them. The dystonia, therefore, seems to arise from a marked imbalance in the ratio of static energy to kinetic energy. This is particularly true during volitional effort. The pronounced hyperkinesis during inaction indicates an unstable condition in the kinetic system, more probably in that portion concerned with automatic associated movements, for the reason that the motor disorders are suggestive of movements of this kind. The disturbance in both the static and kinetic mechanisms partakes of the characteristics indicative of irritation. In addition to the evidence of irritation in these two mechanisms, the analysis points to a disturbance in the rhythm and interrelations of these mechanisms, which, being improperly synchronized in time, force and rate of action, lead to a conflict between hyperstatic and hyperkinetic innervation.

#### IX. ANALYSIS OF A CASE OF CEREBELLAR ATAXIA

The patient was a man forty-one years old whose defects in motility were first observed in infancy. Voluntary efforts of upper or lower extremities, or of the trunk in change of body posture, were always attended by irregular oscillating movements.

His equilibratory defects made locomotion difficult. Incoordination in the speech mechanism imparted a jerky quality to articulation which in consequence was often unintelligible.

At the cinematographic rate of reproduction, the patient demonstrated a marked ataxia in extremities and trunk. The slow motion pictures furnished opportunity for the analysis of the disturbance. When the patient attempted to walk he suddenly lost his equilibrium and fell. As the trunk approached the ground, and an effort at balance was made by the patient, the normal interplay of agonists and antagonists was seen to be defective. The segmental portions of the body as it fell did not follow in sequence nor did they retain their relationship of posture and attitude as seen in the normal. There was evident loss of associative static control. The same group dissociation was seen upon studying the efforts to rise. The extreme disproportion in muscular effort was due to lack of harmonious action between muscle groups. As he attempted to regain the upright position, he sustained for a moment his entire body weight upon his hands; taking advantage of the fact that there was no reduction in dynamic force, he attempted to hurl his trunk upward, thus to attain the upright position without going through the normal sequence of segmental attitudes. With the usual cinematographic speed the details of these pictures would have been beyond visual recognition.

A study of the details of defective motility not associated with equilibration and yet dependent upon synergic control was offered by a series of pictures showing the finger-to-nose test. The hand and finger on approaching the nose showed irregular oscillations which gradually increased toward the end of the act. The oscillations in the upper extremity were due to lack of balance between the components of the synergic units of the arm groups. In analyzing the nature of the rebound phenomenon of Gordon Holmes, in slow motion projection, the wrist when suddenly released by the examiner, rebounded forcibly striking the cheek. This rebound was

due to a failure of the check component—the triceps in this case—to play its part properly in the synergic unit during flexion.

A projection study of the motor phenomenon of the pendular knee reflex shows that this is also due to an inadequate relation between the check and dominant elements in the synergic units producing flexion and extension of the leg on the thigh. Normally the impulse conveyed by tapping the extensor tendon stimulates the quadriceps extensor, the dominant element, and the posterior thigh group, which act as the check element. Working as a synergic unit the two groups during the production of the knee-jerk restrict the motor reaction to one to three oscillations of the leg. This is due to the mutual check action of the two muscle groups affected by the reflex. This fact has been demonstrated (Tilney) by kymographic records in the case of all normal reflexes when, as in this case, the synergic unit for extension and flexion of the leg is dissociated, the mutual check action is lost and this pendulum-like swinging results.

A striking feature of the bradykinetic analysis in this case was the long interval of time that lapsed between the application of the stimulus and the response as seen in the knee-jerk. As the hammer slowly descended upon the tendon of the quadriceps extensor there was a comparatively long interval of latency before the leg began to move.

In summary, the analysis of this case of cerebellar aplasia reveals the fact that the ataxia is due to a failure of the proper coordination in the synergic units of the body and that the disproportionate innervation of the dominant and check elements in each synergic unit leads to the characteristic disorder of cerebellar lesions, *asynergia*. (Figs. 14, 15, 16.)

#### CONCLUSIONS

1. Bradykinetic analysis by means of slow motion pictures furnishes one of the most direct approaches to a clinical study of disturbances of motion.

2. Adventitious elements in motor dis-

turbances are manifest as disorders either in the kinetic or static mechanism.

3. Cinematographic analysis indicates that all purposive movements depend upon the concurrent and synchronized operation of the kinetic and static mechanisms. Such movements are made up of a series of postures beginning with an initial posture and concluding with a terminal posture. This series of postures during a movement may readily be demonstrated by stopping the projection apparatus at each picture either in the slow or normal reproduction. Such an act as taking a step forward then appears to be composed of a series of successive postures.

4. The kinetic mechanism is represented by a neural apparatus capable of correlating the impulses necessary to the production of purposive movements, attitudes and postures, ultimately giving these their proper motor expressions. It, so to speak, prescribes and produces movements and postures for which reason it is a *kinethetic* (causing motion) system.

5. The static mechanism is represented by a neural apparatus capable of correlating the impulses necessary to the proper maintenance of postures. Ramsay Hunt has graphically illustrated the relation of posture to motion in his expression that "movements are followed by their attendant postures like shadows." Analysis by the slow moving pictures verifies this conception. The static mechanism, so to speak, controls the postures which follow movements like shadows, stabilizing them through all their phases. In this sense and because it maintains posture, it is a *statothetic system*.

6. From such evidence as is at present available, it seems warranted to conceive of a static arc representing the statothetic system with its chief center in the cerebellum, and a kinetic arc representing the kinesi-thetic system whose centers are in the end-brain. The trend of recent opinion would allocate the primordial center for the kinetic arc (paleokinesis—Hunt) to the corpus striatum or basal forebrain ganglion.

7. The disorders of motion investigated in

this study, including choreiform movements in chronic degenerative chorea and astasia abasia, cerebellar ataxia in a case of cerebellar aplasia, intention tremor in multiple sclerosis, and dystonia in dystonia musculorum deformans, may be attributed to disorganizations in the two fundamental neural arcs already described.

8. Choreiform movements in degenerative chorea, upon analysis, appear to be due to a hyperkinetic disorder resulting in the sudden productions of postures and attitudes directly expressive of the emotions of fear, anger, disgust, etc. The static mechanism is affected to a lesser degree as shown in the instability of posture indicating an imperfect association of the synergic units. Choreiform movements in astasia abasia are likewise based principally upon hyperkinetic defects. The resulting disorders of motion produce postures and attitudes expressive of the emotions. In this case these emotions are more highly complex than in degenerative chorea, and indicate a more acutely conscious and psychic elaboration of fear.

9. Cerebellar ataxia and intention tremor, upon analysis, both appear to be due to essentially the same defect limited to the static mechanism. The motor disturbances in these conditions are produced as a result of a disorganization in the proper relation of the synergic units of the body.

10. The dystonias, upon analysis, are clearly revealed as hyperkinetic and hyperstatic in nature. The normal concurrence in these two streams of static and kinetic innervation is imperfect or wanting. These mechanisms appear to be affected by pronounced irritation or lack of proper inhibition.

11. The foregoing suggestions on the basis of bradykinetic analysis are offered with the desire of furnishing an anatomical and physiological background for certain motor disorders and at the same time of calling attention to the seemingly essential relationship of the static and kinetic mechanisms in all purposive motion. Much further study is needed in the development of these conceptions before they may be advanced as more than working hypotheses.



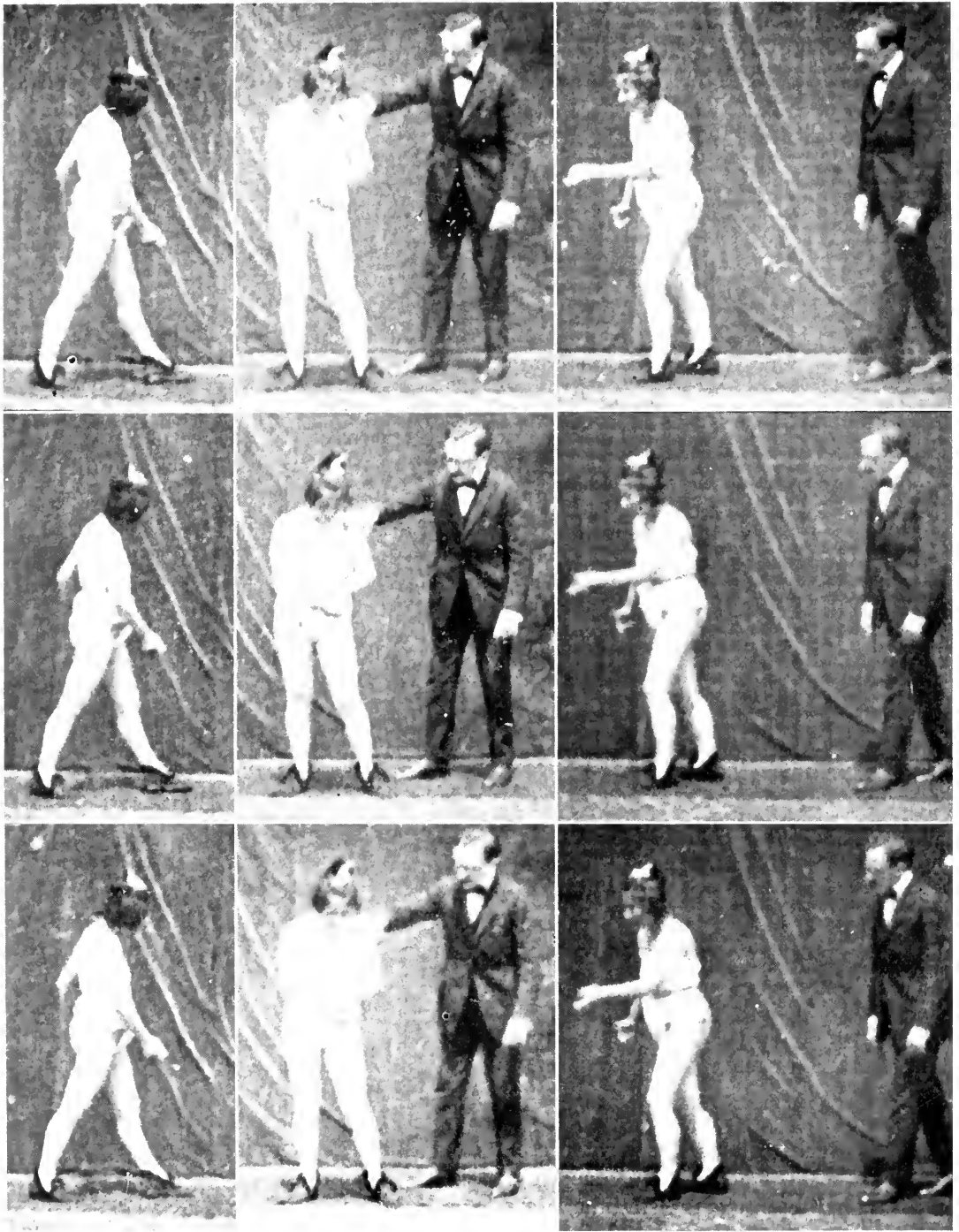


FIG. 1. Bradykinetic Analysis in a Case of Chronic Degenerative Chorea with Athetotic, Choreiform and Attitudinizing Elements.

What appeared by normal projection as purposeless, meaningless movements, by bradykinetic analysis are seen to be gesticulations, expressions of definite acts of going, of giving; and attitudes and gestures symbolizing emotions of shame, coyness,

turning away, etc. The hyperextension of the left leg at the knee is seen in the picture. Athetotic (polypoid) movements of the fingers are indicated. Facial grimacing is indistinctly discernible in the photographs though clearly seen on the screen.



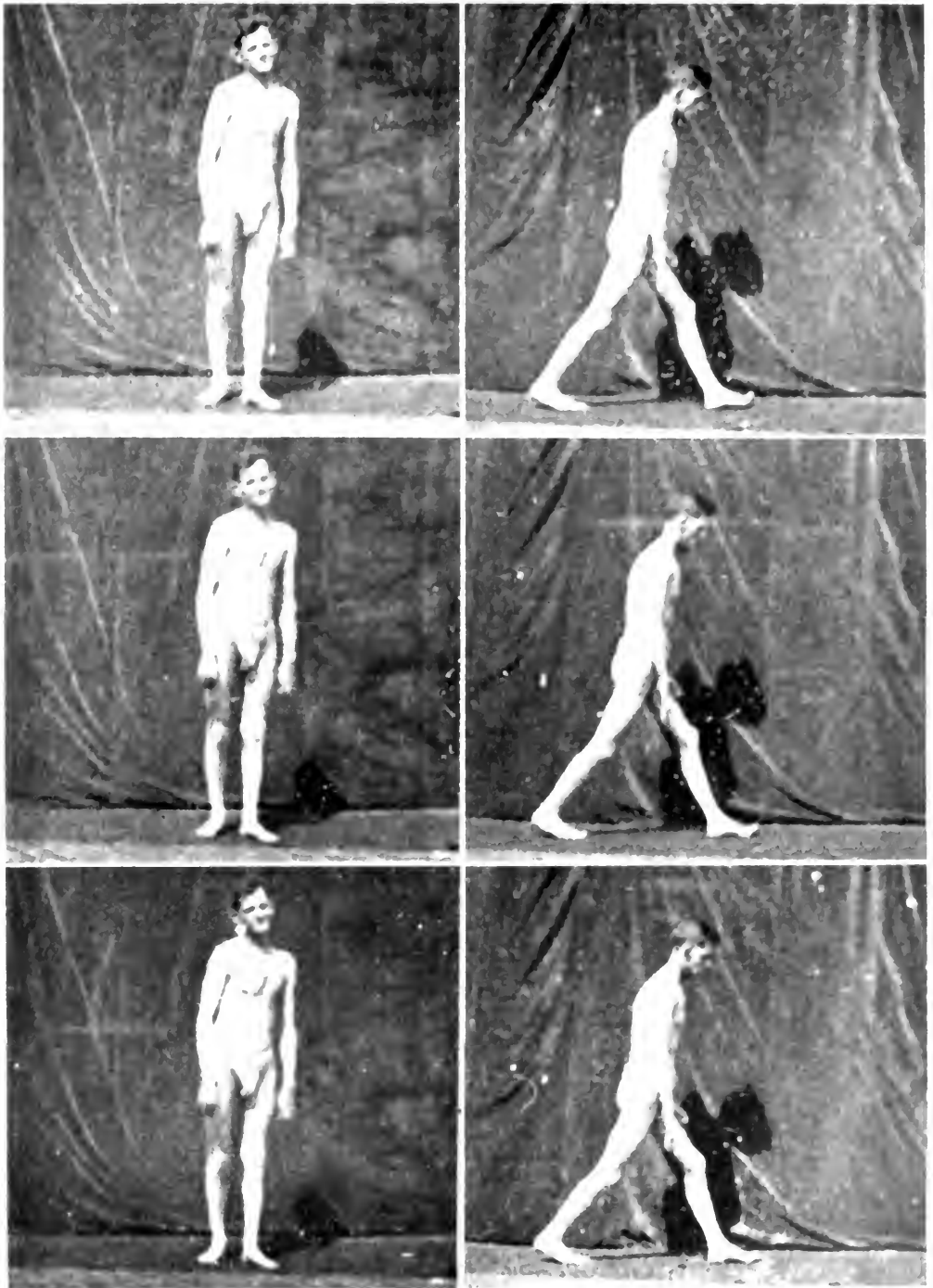


FIG. 2. Bradykinetic Analysis in a Case of Chorea Minor.

Torsion movement involving upper extremities and thoracic musculature: pronator position of hand at forearms. Extensor position of leg, too, not Babinski, however. Overextension of foot in walking, almost a constant feature of gait in dystonia, is not seen in above; on the screen, however, it is occasionally observed in this patient but to a far less degree.

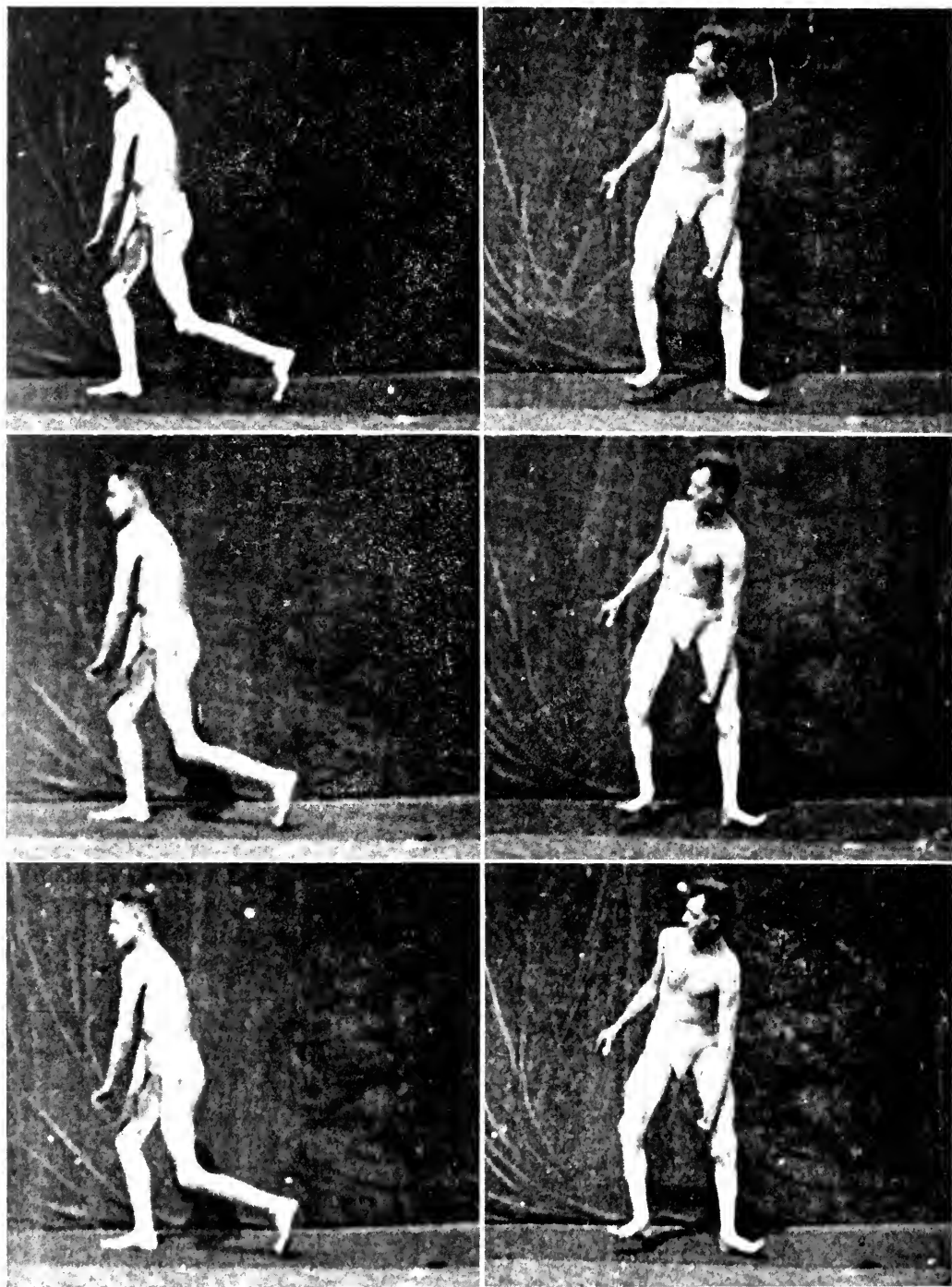


FIG. 3. Same Case as figure 2.

Gait with overflexion at the knees and pronator position of forearm with right arm fixed on thigh during locomotion give dystonic character

to attitude; attitudinizing as seen in act of hurling an object. (Compare with figure 9).



FIG. 4. Bradykinetic Analysis of a Case of Multiple Sclerosis.  
 (From *Journal of Neurology*, 1925, 10, 185.)

Observe dyspraxia even as patient attempts to place his upper extremities in position for approximation of the widely separated elbows. The abnormal morphology of group movement becomes more evident as patient attempts to bring his fingers together. The arms shoot far beyond the point desired, each

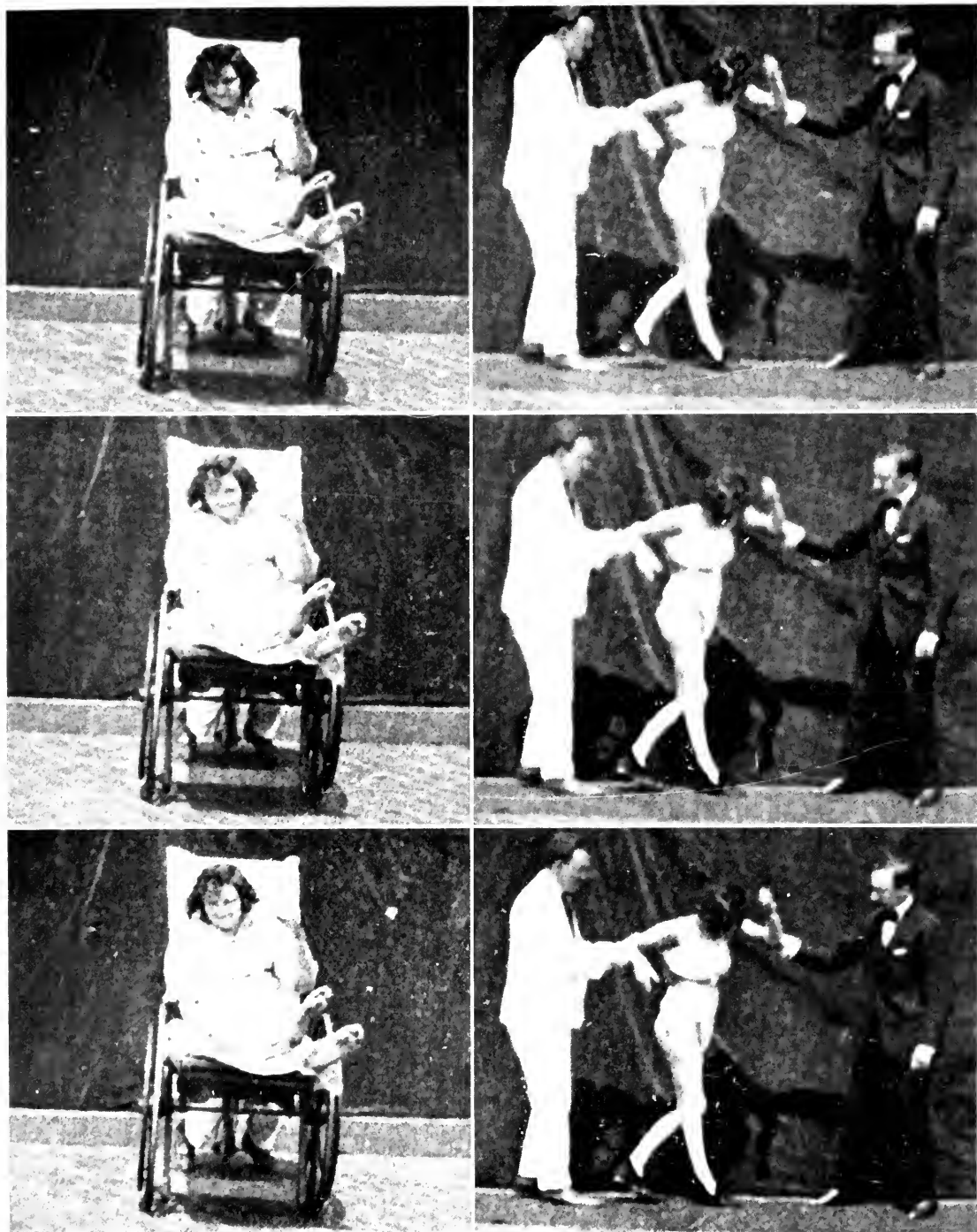


FIG. 5. Bradykinetic Analysis in a Case of Astasia-abasia with Excessive Motor Agitation.

Motor manifestations classically those of psychic origin. With patient seated the foot and toes show tendency to plantar contraction there being no paralysis of extensors and no true contractures of flexors. The upper and lower extremities are in constant

movement showing distinctly a pattern; static and kinetic mechanisms act normally and in unison. Upper extremities are engaged in rhythmic movements imitative of those of flying. Vermicular wave described in text is not discernible in photograph.

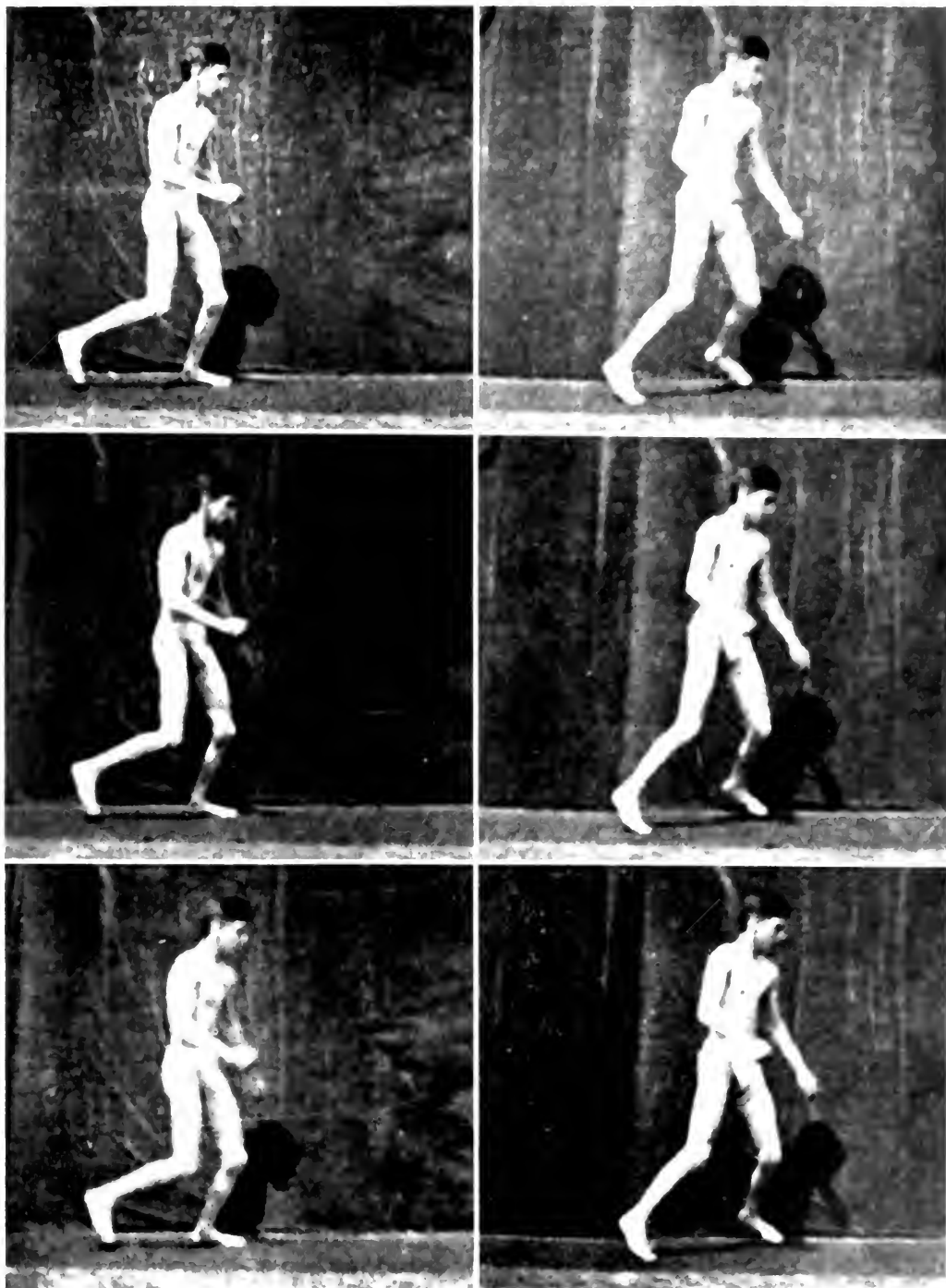


FIG. 6. Bradykinetic Analyses of a Case of Paralysis of One Limb. (A. 70-1)

The above picture is that of the brother, the first to be afflicted, and showing the imperfect state of habitus, characteristic inward rotation at knee, common posture.



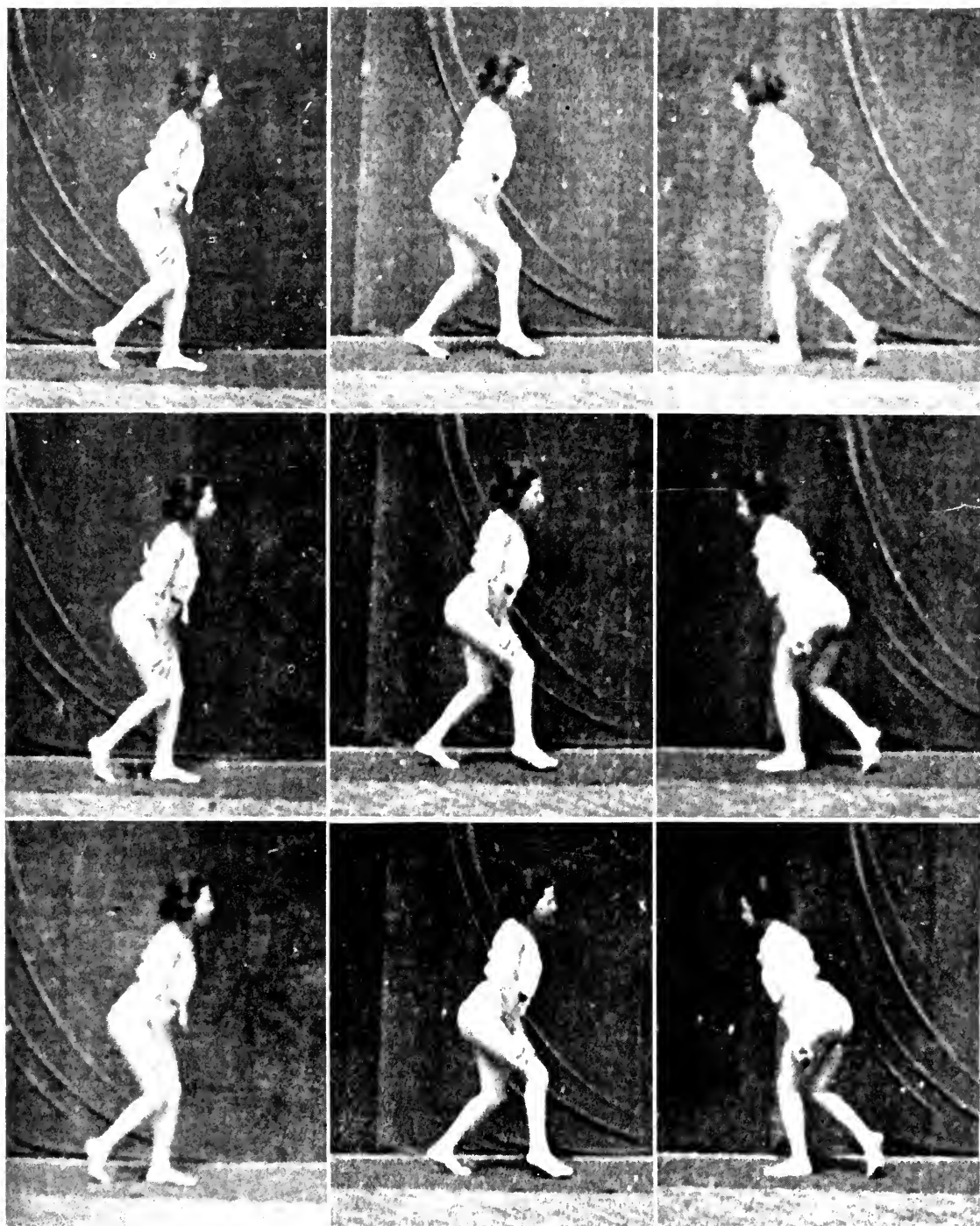


FIG. 7. Bradykinetic Analysis in a Case of Familia I Dystonia Musculorum; One Sister.

Symptoms more pronounced than in the case of the brother (preceding picture). Observe lordosis, flexion at hip and knee. Flexure contractures of right hip and knee joints are fixed by muscle changes. Inward rotation knee and hip, also hyperextension

at ankle while walking, together with pronator position of forearm and hand are shown in the picture. The mechanism in muscular group action is brought out in the animated series on the screen.

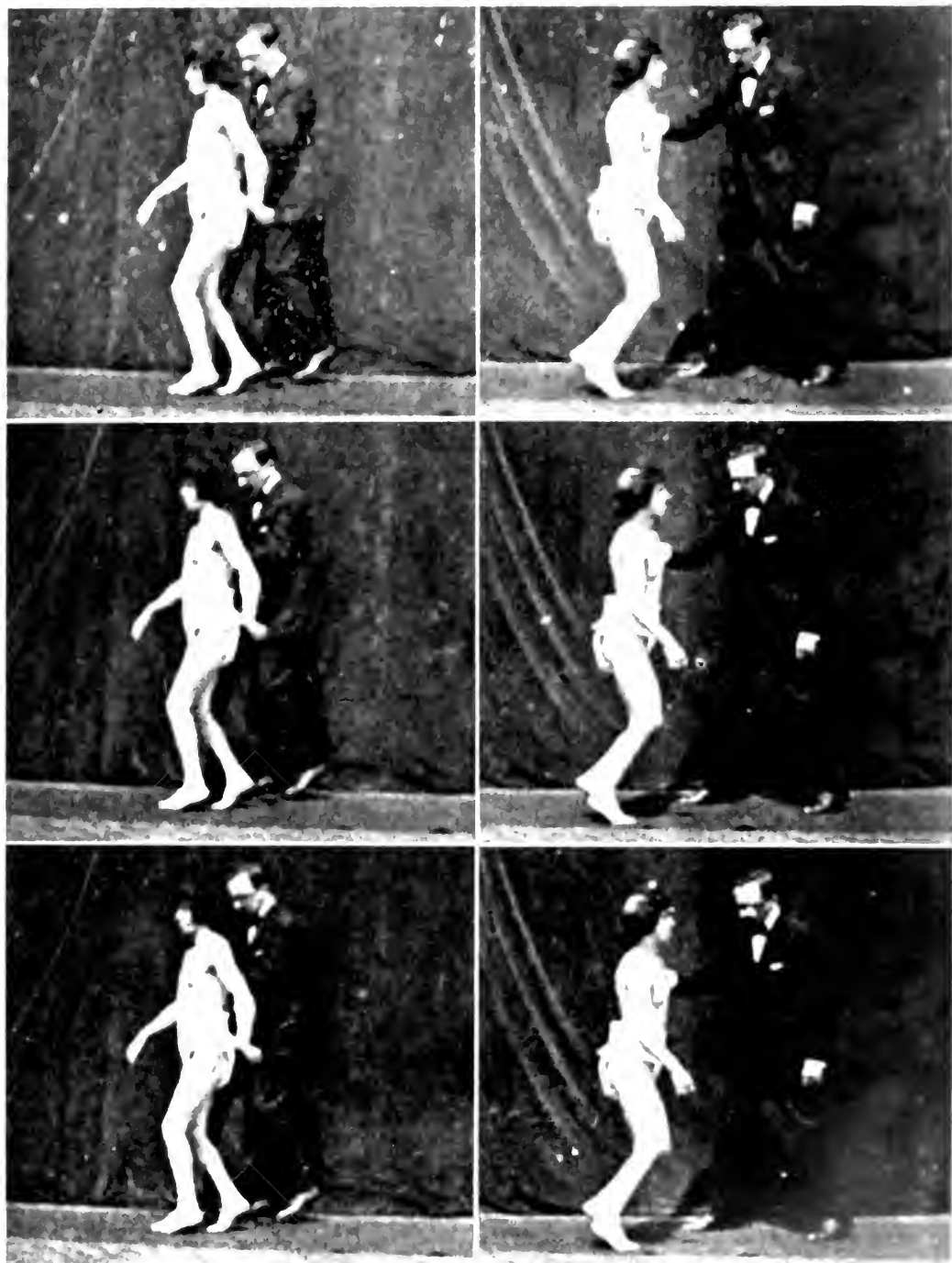


FIG. 8. Bradykinetic Analysis of a dance (Pamela Lee).  
Flexor fixation at knee, common position of the feet, and position of the

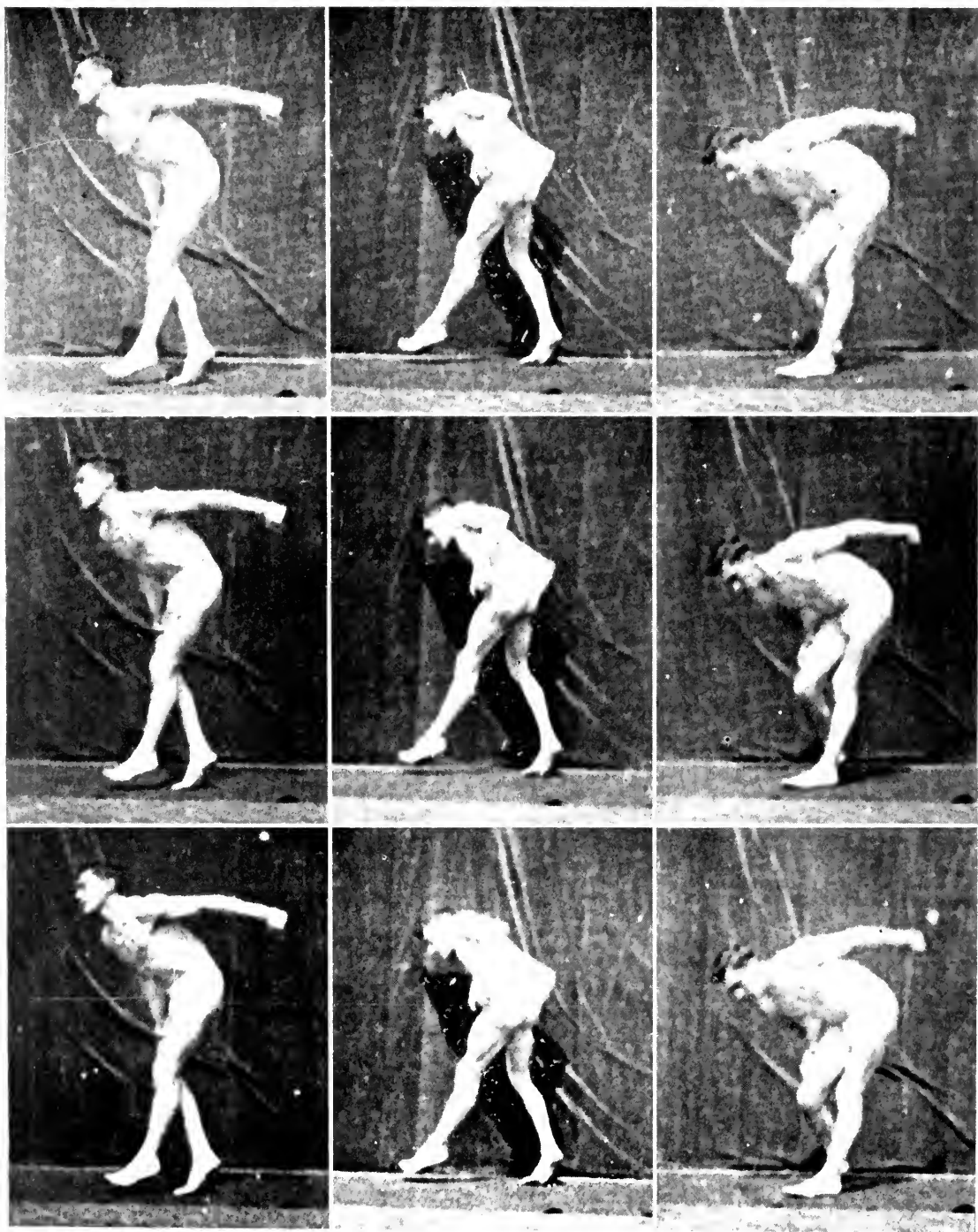


FIG. 9. Bradykinetic Analysis in a Case of Dystonia Musculorum Deformans. Involvement of All Groups of Muscles and True Hypertrophies.

Bizarre distortions of movement. Characteristic positions. Plantar flexion at ankles in walking. In some position inward rotation at knee. Trunk muscles also involved. Body thrown violently forward and movement intensified by upward projection by extensors of hip, knee and ankle. Hand resting on thigh to restrict extreme sudden flexion at hip. Some ten-

denity to pelvic torsion. Force in extension movements so great as to literally hurl the body forward. Sudden uncontrolled flexor and torsion movements give impression patient is about to hurl heavy object. Suggestion of sudden release of kinetic energy not controlled in static fixation. There is no permanent fixation by contractures in this case.



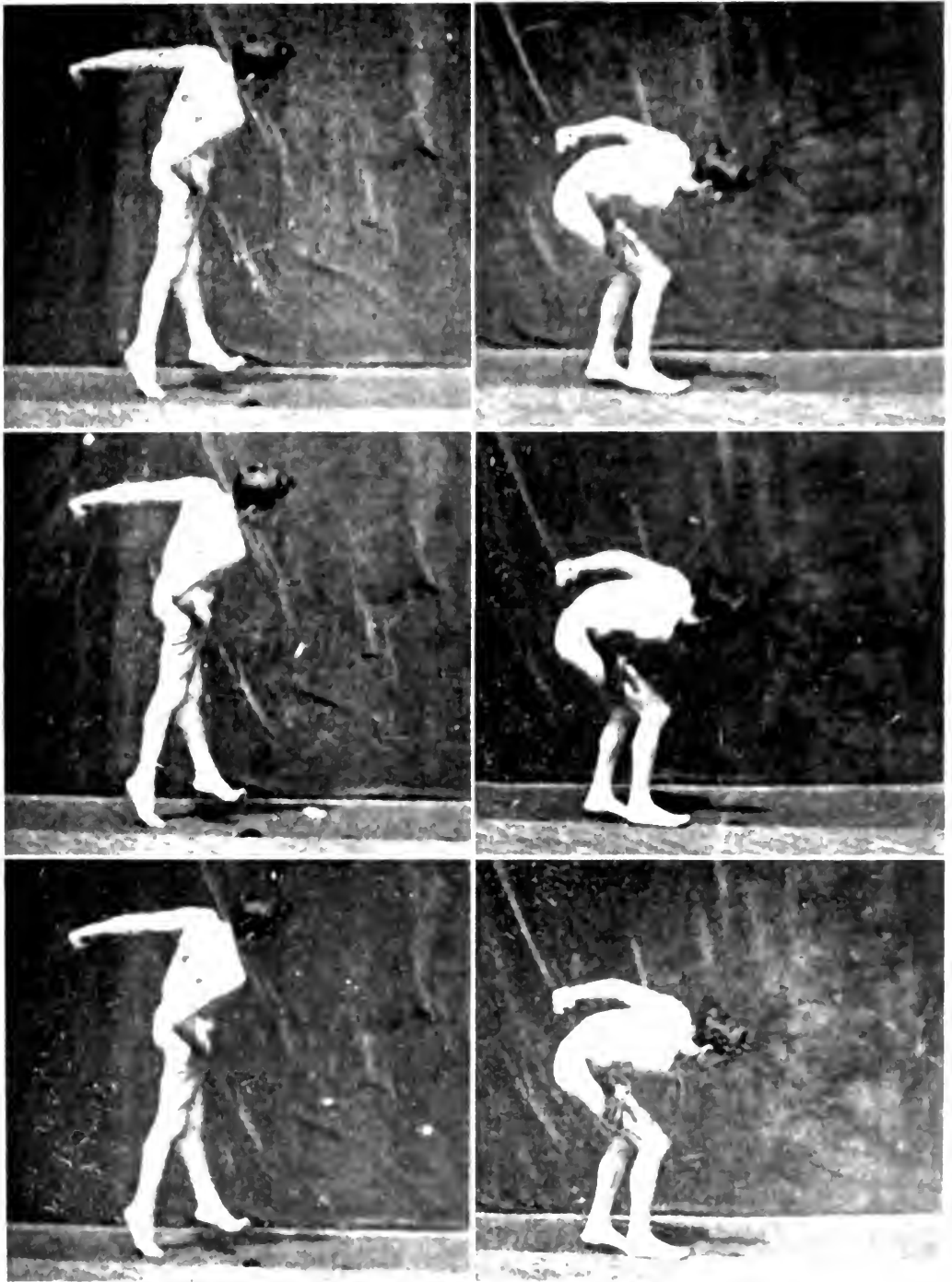


FIG. 10. Bradykinin. Analysis in a case of Dystonia. Same as figure 6. Observe better control of the swing.

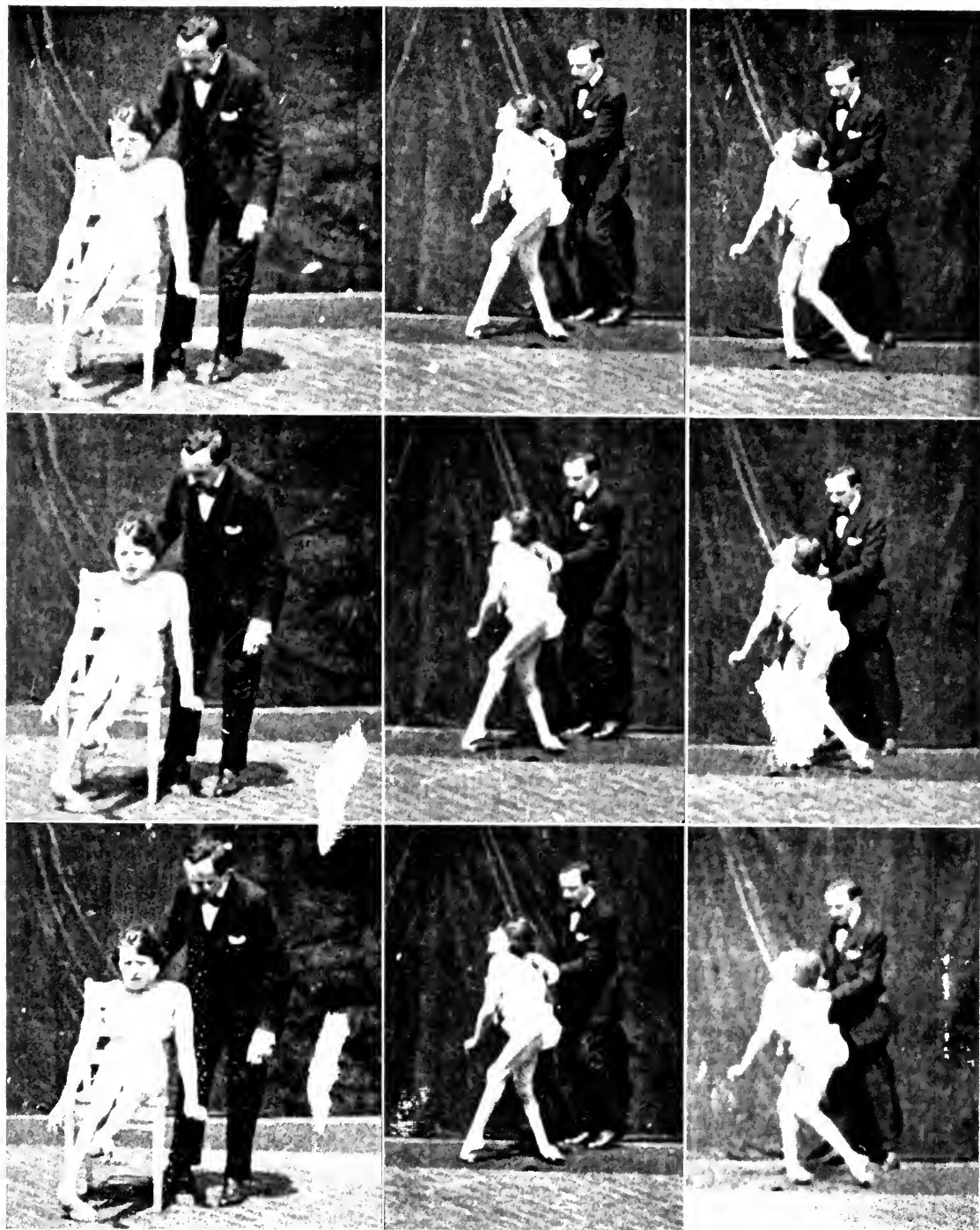


FIG. 11. Bradykinetic Analysis in a Case of Dystonia Musculorum Deformans with "Dromedary Attitude": Semi-lunar Foot.

Extreme deformities of feet; girl walks on dorsal surfaces of feet. Extensor and equinus positions have become "fixed," in less intense degree "fixation" positions in flexion have also developed at hip and knee. Lower extremities below knee relatively atrophic from partial disuse after ankylosis changes though the tibia and calf groups are still in constant myotonic activity as far as the joint changes permit. Upper extremities are in constant motion and all

muscles hypertrophied. The trapezii are especially active causing ceaseless clonic extensor movements of the head. There is extreme deformity of trunk due to fixation by domination of certain muscle groups of the trunk and pelvis. Forearms are in characteristic positions. In the moving pictures a distinct rhythm of the paralysis agitans type can be observed in the movements of the forearms and hands.

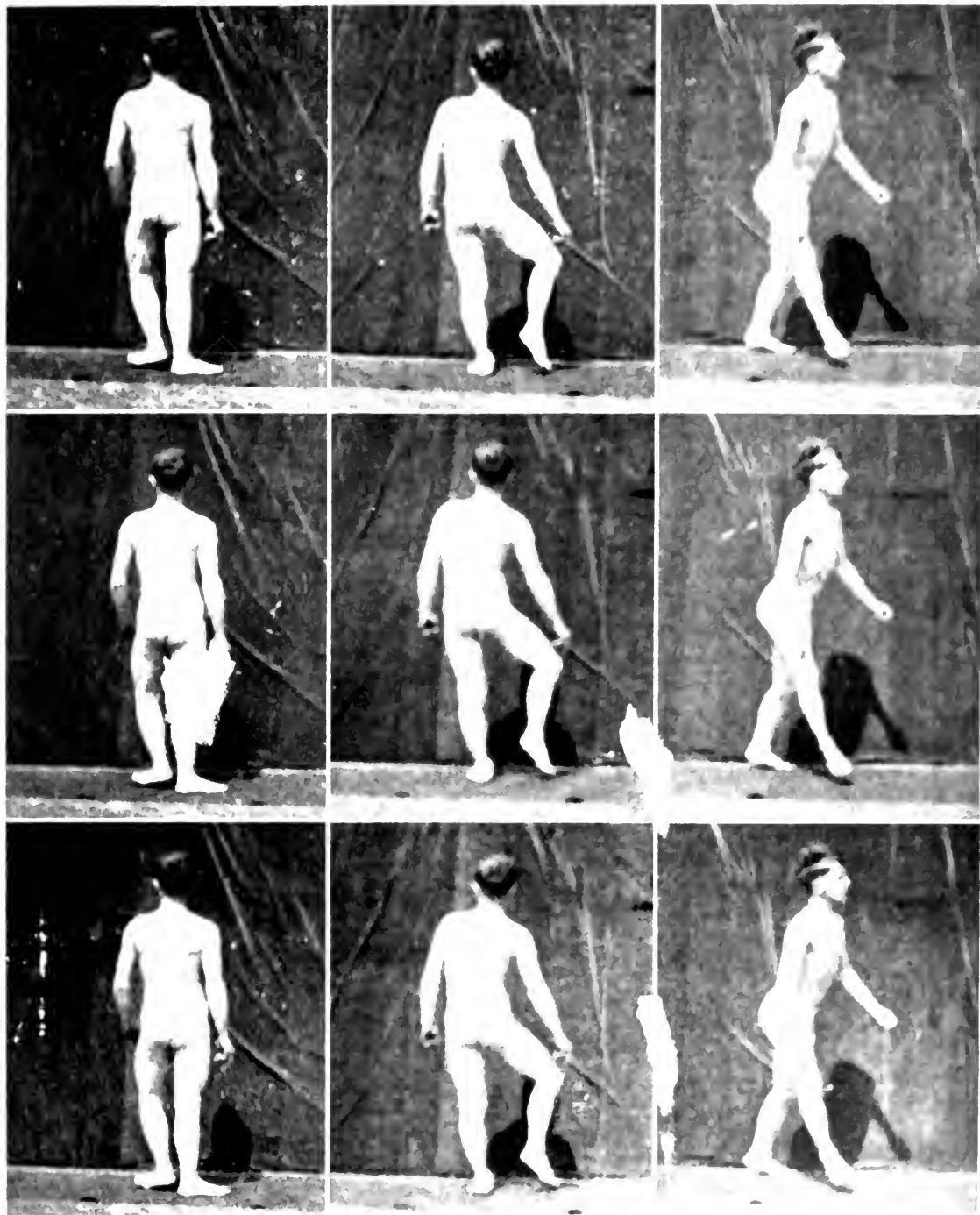


Fig. 12 Bradykinetic Analysis in a Case of Dystonia Muscles Limbica. (1937)  
 Characteristic attitudes: external rotation of the legs  
 (sagittal view).

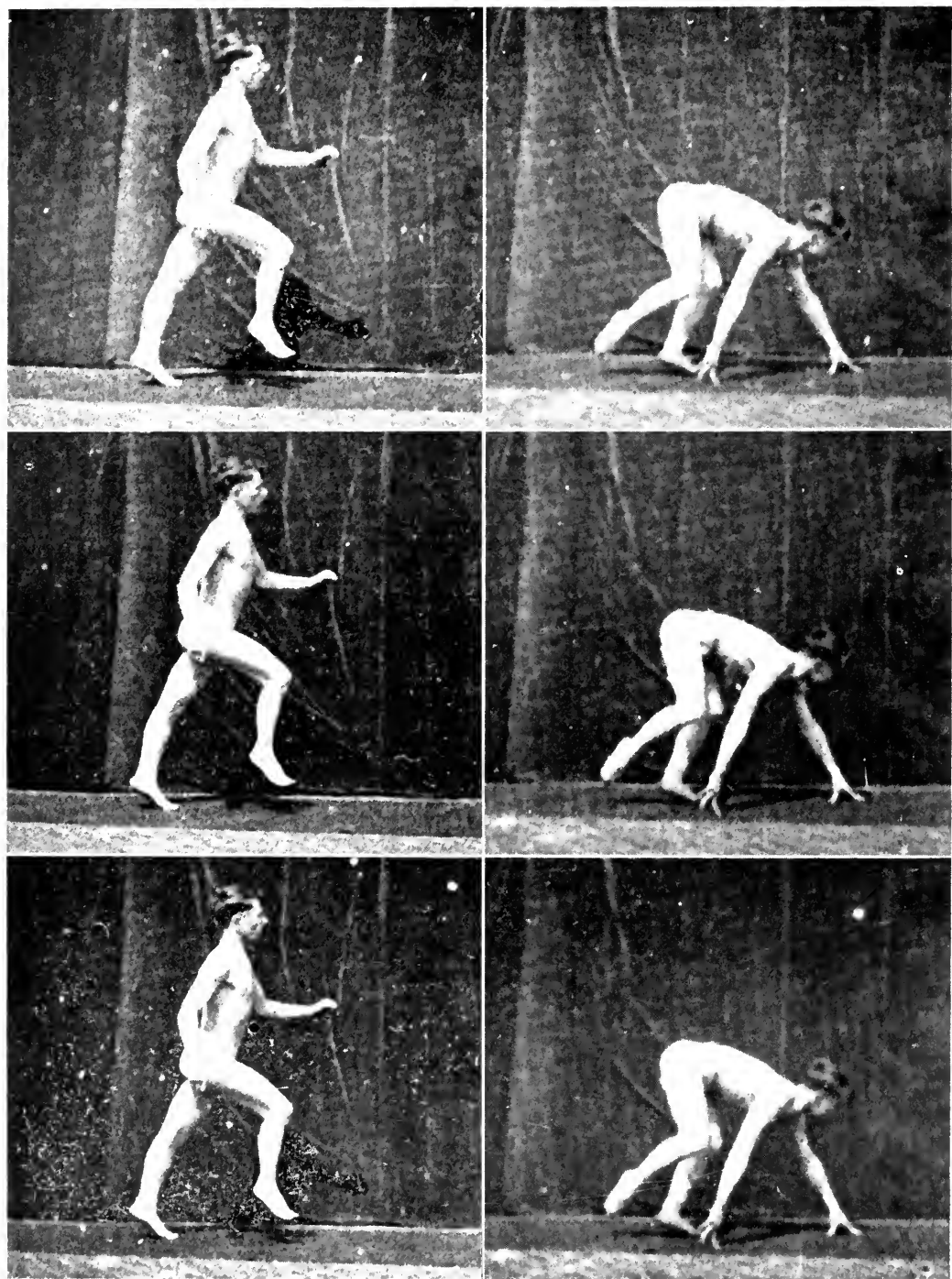


FIG. 13. Same as figure 12.

Showing marked improvement of muscle control and type of exercise helpful in re-education; demonstrating also as patient advances resting on fingers, ball of foot and toes, characteristic dystonia attitudes. This position on "all fours" as patient moves forward

emphasizes the special deformity due evidently to defective postural fixation in the motor conflict which shoots, so to say, the pelvis and trunk upward in progression.

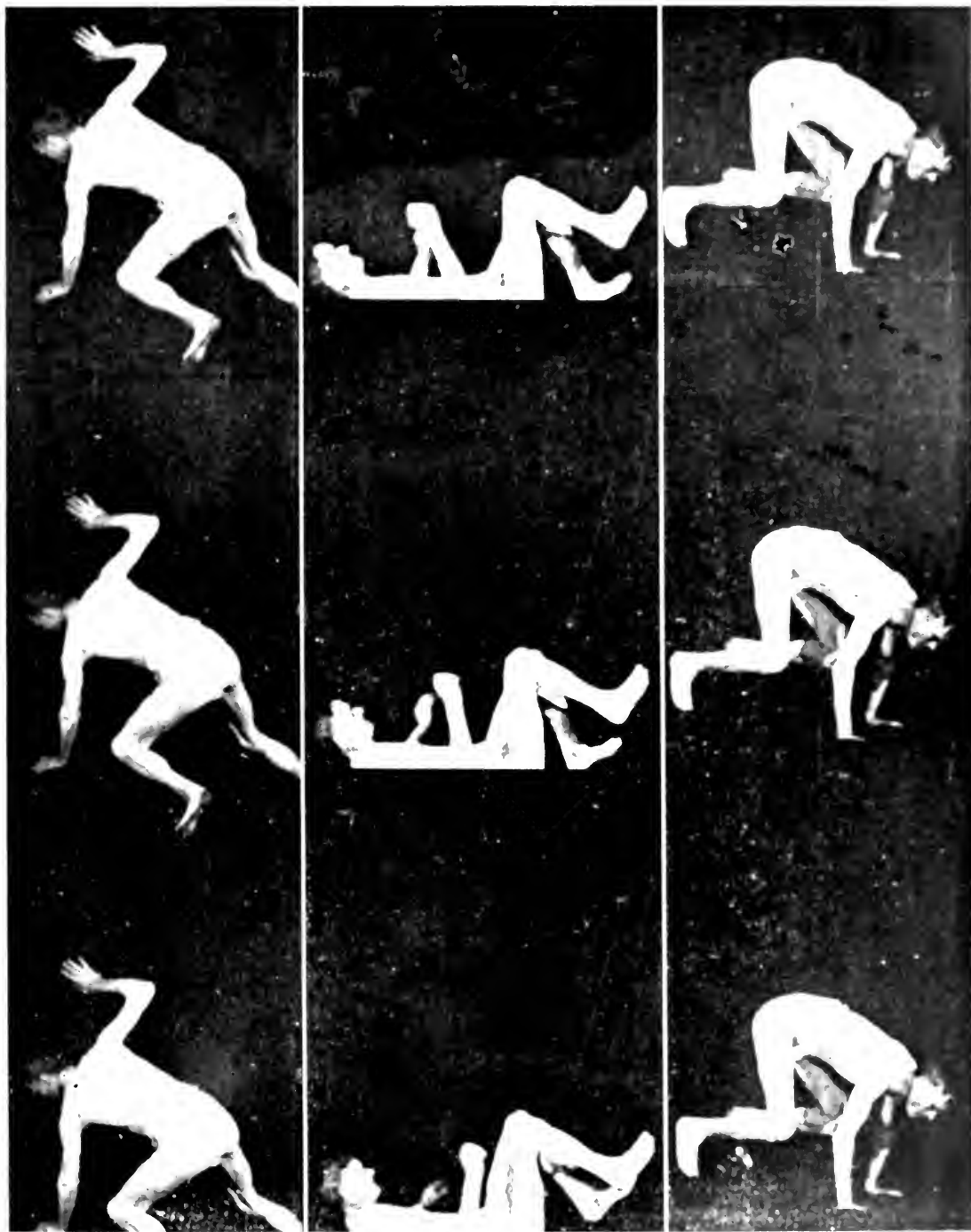


FIGURE 10.10. As the actor approaches the end of the sequence

As final approach is completed, the actor's torso is extended, and the acrobats and actors are in a state of tension. Some of the dissonance is seen upon the actor's approach.



FIG. 15. Same Case as Figure 14; Showing Finger to Finger Test.

Careful observation shows the so-called tremor of the multiple sclerosis type to be the result of defective cerebellar function. The analysis by slow motion photography clearly defines the dissociation of the synergic unit. The serial pictures, of which

the above illustrations are necessarily only fractional units, show the defective interplay of the agonist and antagonist and its corresponding check component thus mechanically defeating attainment of the purposeful movement.



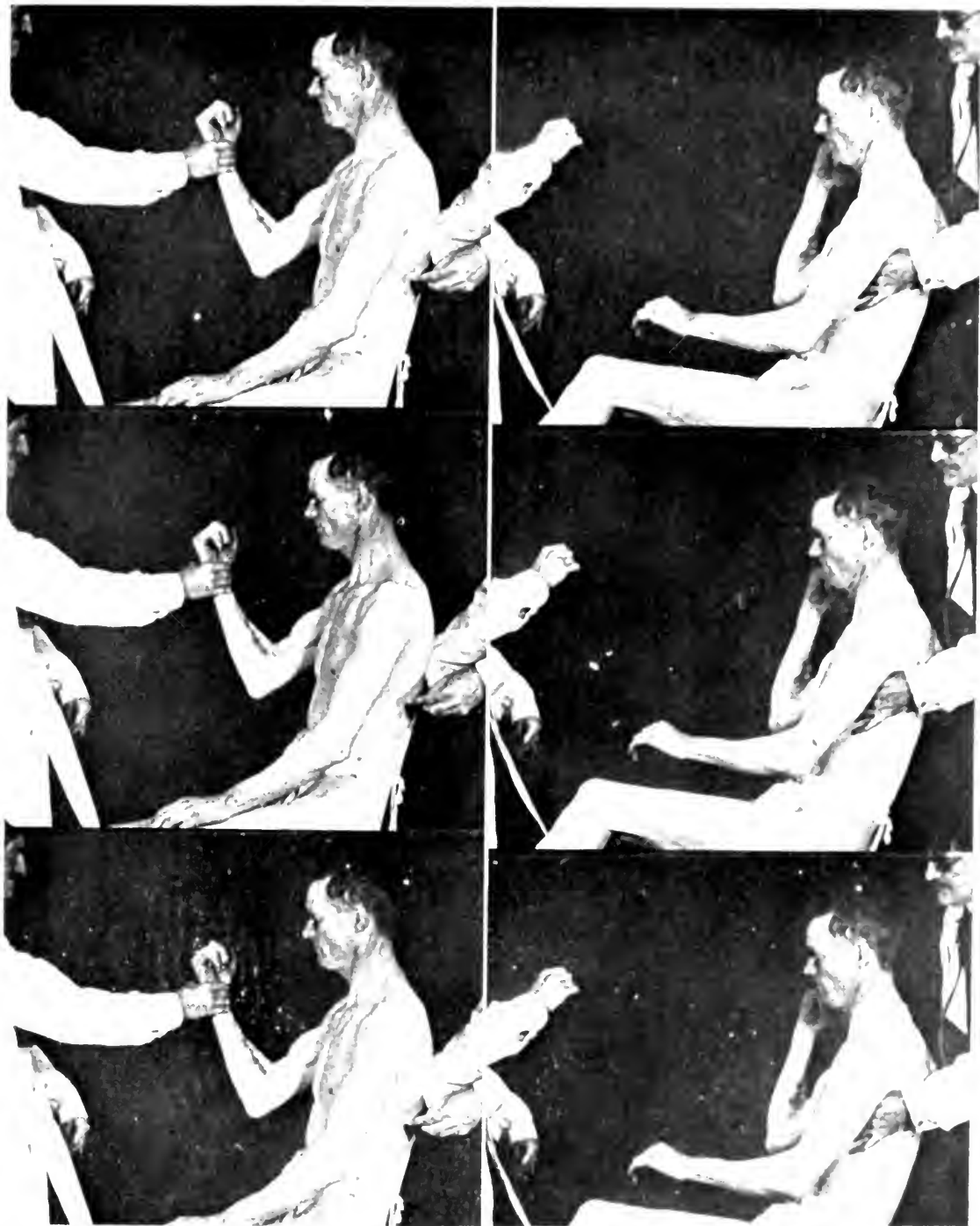
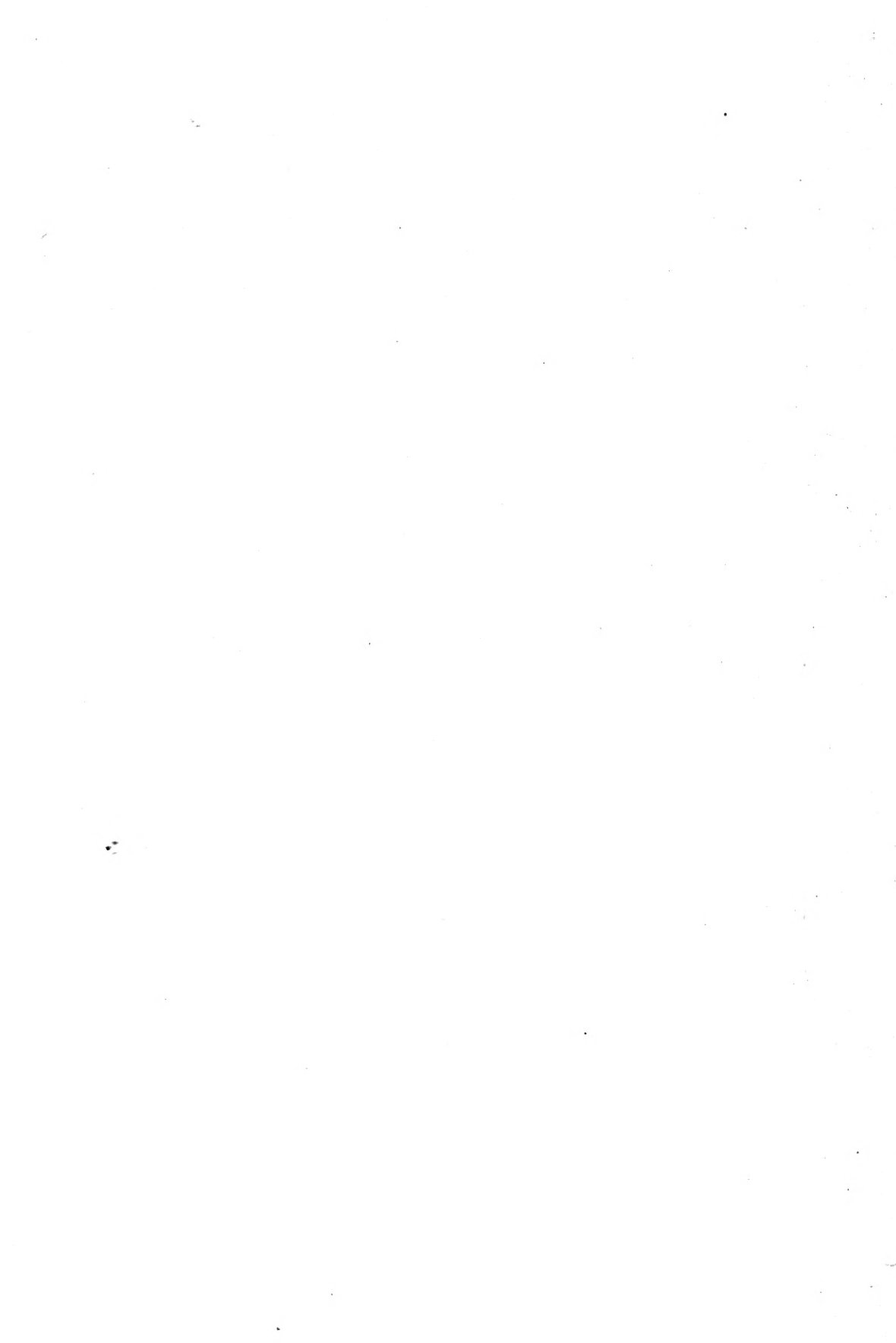


FIG. 10. Same Case as Figure 11. Shown (1) A

As the examiner tests the patient's arm, the patient attempts to extend the flexor arm of the arm. At the same time, the examiner suddenly releases the wrist, the arm recoils and rebounds forcibly, striking his head. This is shown by analysis in slow motion as seen in the film.





# An Interpretation of the Posture of Parkinsonian Syndromes in Terms of the Neuro- Muscular Mechanism

BY

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NEW YORK CITY

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AN INTERPRETATION OF THE POSTURE OF PARKINSONIAN SYNDROMES IN TERMS OF THE NEUROMUSCULAR MECHANISM.

By WALTER M. KRAUS, A.M., M.D.,  
NEW YORK CITY.

I. THE POSTURE OF THE PARKINSONIAN SYNDROME

AT the present time the positions of the various parts of the body in the Parkinsonian syndrome, when described only in terms of muscle movements, that is, of flexion, extension, etc., give no notion of uniformity, no notion of a homogeneous reaction due to disease of the nervous system. The position of the fingers illustrates this very clearly. They are usually flexed at the metacarpo-phalangeal joints and extended at the interphalangeal joints. Gowers has called this the interosseal position. As to the rest of the body, it may be said in general that the arms are held flexed and adducted, that in severe cases the neck and trunk are flexed, and that there is flexion at the hip and at the knees. In the rare instances where contracture affects the feet, extension occurs, producing a pes equinus or equino-varus. In the forms of the disease due to arteriosclerosis involvement of the feet is not common. However, in those forms due to epidemic encephalitis a pes equinus or pes equino-varus is often found.

Certainly it is difficult to interpret such a mixture of flexion, extension, etc., as indicative of a uniform reaction of the nervous system or of the muscular system due to disease. Nor do we find this so expressed in the present descriptions. However, if movement is described in terms of the neuromuscular instead of the muscular mechanism, that is, if we take into consideration peripheral motor neurones as innervators of muscles, the grouping of these neurones and their control by the spinal cord as well as the embryology and grouping of muscles, we find that the picture is greatly simplified.

Both the nerves and muscles of the trunk and extremities are divisible into a large dorsal and a large ventral group. (Tables 1, 2, 3, 4.) In the Parkinsonian syndrome it is very easy to show that the ventral group becomes more active than the dorsal group. An imbalance exists between these two large groups in spite of the fact that no paralysis of voluntary power is present. This imbalance is due to abnormal innervation of antagonistic groups of muscles.

The nervous system surely is so constructed

that it may produce various muscular patterns. These patterns or positions are due to variations in the innervation of antagonistic groups of muscles. For example, in post hemiplegic contracture of the arm, there is flexion at the elbow. The biceps is more powerfully innervated than the triceps. In decerebrate rigidity there is extension at the elbow. The opposite conditions obtain. The triceps is more powerfully innervated than the biceps. These patterns are constants.

The force which activates muscles in these patterns is tonus. For example, under certain experimental or clinical conditions, the muscles of the body assume a pattern which has been termed decerebrate rigidity by S. A. K. Wilson<sup>1</sup> and which was previously designated by Sherrington<sup>2</sup> as the antigravity position. So long as tonus exists this position exists. When tonus is eliminated the position disappears. In the Parkinsonian syndrome abnormalities of tone usually exist. There is never a complete absence of tone, flaccidity. Tone is sometimes normal, usually increased. There is a second factor. The pathological process has liberated parts of the nervous system capable of producing an abnormal posture or muscular pattern due to abnormality of innervation of antagonistic groups of muscles. Into this pattern tone flows. The activity of hyoscine in diminishing the severity of this abnormal posture or pattern by reducing tone forms a proof of the explanation given.

TABLE I.  
DIVISION OF THE NERVES OF THE EXTREMITIES INTO VENTRAL AND DORSAL GROUPS

UPPER EXTREMITY	
ORIGIN	NERVES
BRACHIAL PLEXUS	Dorsal trunks (Posterior cord)
	Dorsal scapular Long thoracic Suprascapular Subscapular (2) Thoraco-dorsal Axillary Radial
	Ventral trunks (Lateral and medial cords)
	Nerve to subscapularis Anterior thoracic Musculospiral Median Ulnar
LOWER EXTREMITY	
LUMBOSACRAL PLEXUS	Dorsal trunks
	Sacral plexus Sciatic Tibial Femoral Obturator Sartorius Iliotibial Saphenous Tibial Femoral Obturator Sartorius Iliotibial Saphenous
	Ventral trunks
	Sacral plexus Sciatic Tibial Femoral Obturator Sartorius Iliotibial Saphenous Tibial Femoral Obturator Sartorius Iliotibial Saphenous

TABLE II.

## AXIAL MUSCLES

<i>Muscles of the Back</i>	<i>Ventral</i>	<i>Dorsal</i>
Serratus posterior superior.....	x	
Serratus posterior inferior.....	x	
Splenius .....	x	
Sacrospinalis .....	x	
Iliocostalis .....	x	
Longissimus .....	x	
Spinalis dorsi .....	x	
Semispinalis .....	x	
Multifidus .....	x	
Obliquus capitis inferior .....	x	
Obliquus capitis superior .....	x	
Rectus capitis posterior major.....	x	
Rectus capitis posterior minor.....	x	
Rotatores .....	x	
Interspinales .....	x	
Intertransversarii .....	x	
Trapezius .....	x	

*Muscles of the Neck*

Scalenus anterior .....	x
Scalenus medius .....	x
Scalenus posterior .....	x
Longus capitis .....	x
Rectus capitis anterior .....	x
Longus colli .....	x
Rectus capitis lateralis .....	x
Sterno-kleido-mastoid .....	x

*Muscles of the Thorax*

Intercostales .....	x
Levatores costarum .....	x
Subcostales .....	x
Transversus thoracis .....	x

*Muscles of the Abdominal Wall*

Obliquus externus abdominis .....	x
Obliquus internus abdominis .....	x
Cremaster .....	x
Transversus abdominis .....	x
Pyramidalis abdominis .....	x
Rectus abdominis .....	x
Quadratus lumborum .....	x

*Muscles of the Perineum*

Sphincter ani externus .....	x
Corrugator cutis ani.....	x
Transversus perinei superficialis .....	x
Bulbocavernosus .....	x
Ischiocavernosus .....	x
Sphincter urethrae membranaceae .....	x
Transversus perinei profundus .....	x

*Muscles of the Pelvis*

Levator ani .....	x
Coccygeus .....	x

TABLE III.

## MUSCLES OF THE UPPER EXTREMITY.

<i>Dorsal</i>	<i>Ventral</i>
1. Levator scapulae	
2. Serratus anterior	
3. Rhomboideus major	
4. Rhomboideus minor	
5. Supraspinatus	
6. Infraspinatus	
7. Teres minor	
8. Deltoid	
9. Subscapularis	
10. Teres major	
11. Latissimus dorsi	
	12. Subclavius
	13. Pectoralis major
	14. Pectoralis minor
	15. Biceps brachii
	16. Brachialis*
	17. Coracobrachialis
18. Brachio-radialis	
19. Extensor carpi radialis longus	
20. Extensor carpi radialis brevis	
21. Supinator	
22. Extensor pollicis longus	
23. Extensor indicis proprius	
24. Abductor pollicis longus	
25. Extensor pollicis brevis	
26. Extensor communis digitorum	
27. Extensor carpi ulnaris	
28. Extensor minimi digiti quinti	
29. Anconeus	
30. Triceps	
	31. Pronator teres
	32. Flexor carpi radialis
	33. Palmaris longus
	34. Flexor digitorum sublimis
	35. Flexor digitorum profundus
	36. Flexor pollicis longus
	37. Pronator quadratus
	38. Lumbrical 1
	39. Lumbrical 2
	40. Lumbrical 3
	41. Lumbrical 4
	42. Abductor pollicis brevis
	43. Opponens pollicis
	44. Flexor pollicis brevis. Lateral head
	45. Flexor pollicis brevis. Medial head
	46. Flexor carpi ulnaris
	47. Adductor pollicis obliquus
	48. Adductor pollicis transversus.
	49. Interosseus volaris 1
	50. Interosseus volaris 2
	51. Interosseus volaris 3
	52. Interosseus dorsalis 1
	53. Interosseus dorsalis 2
	54. Interosseus dorsalis 3
	55. Interosseus dorsalis 4
	56. Opponens digiti quinti
	57. Flexor digiti quinti brevis
	58. Abductor digiti quinti

\* Supplied by both ventral and dorsal nerves.

TABLE IV.  
MUSCLES OF THE LOWER EXTREMITY.

*Dorsal*

*Ventral*

1. Iliacus
2. Psoas major
3. Psoas minor
4. Pectineus\*
5. Sartorius
6. Rectus femoris
7. Vastus lateralis
8. Vastus medialis
9. Vastus intermedius
10. Tensor fasciae latae
11. Glutaeus minimus
12. Glutaeus medius
13. Piriformis
14. Glutaeus maximus
15. Biceps femoris (shorthead)

16. Biceps femoris (longhead)
17. Semitendinosus
18. Semimembranosus
19. Adductor magnus
20. Obturator externus
21. Adductor longus
22. Adductor brevis
23. Gracilis
24. Obturator internus
25. Superior gemellus
26. Inferior gemellus
27. Quadratus femoris

28. Tibialis anterior
29. Extensor hallucis longus
30. Extensor digitorum longus
31. Peroneus tertius
32. Peroneus longus
33. Peroneus brevis
34. Extensor digitorum brevis

35. Gastrocnemius
36. Soleus
37. Plantaris
38. Popliteus
39. Tibialis posterior
40. Flexor digitorum longus
41. Flexor hallucis longus
42. Quadratus plantae
43. Abductor digiti quinti
44. Flexor digiti quinti brevis
45. Opponens digiti quinti
46. Plantar interosseus 1
47. Plantar interosseus 2
48. Plantar interosseus 3
49. Dorsal interosseus 1
50. Dorsal interosseus 2
51. Dorsal interosseus 3
52. Dorsal interosseus 4
53. Adductor hallucis
54. Lumbrical 1
55. Lumbrical 2
56. Lumbrical 3
57. Lumbrical 4
58. Abductor hallucis
59. Flexor digitorum brevis
60. Flexor hallucis brevis

\* Supplied by both ventral and dorsal nerves.

In order to establish the muscular pattern it is necessary to consider the position of the various parts of the body in both unilateral and bilateral Parkinsonian syndromes.

### A. The Position of the Hand

In the Parkinsonian syndrome the fingers are usually extended at the phalangeal and flexed at the metacarpophalangeal joints. The thumb is slightly adducted, certainly not extended. This position is entirely dependent upon the activities of the ventral intrinsic muscles of the hand. All of these muscles are innervated by the ventral median and ulnar nerves. (Table 3.) Were the dorsal muscles controlling the fingers at all hyperactive we should have a position approach-

ing that of a clawhand which is indeed opposite to that which occurs in the Parkinsonian syndrome.

When the postural defect is more exaggerated, the long flexors of the thumb and fingers bring them into a position of flexion and the hand slowly assumes the classical position found in the hypertonic type of hemiplegia. The remainder of the arm is flexed at the wrist and elbow joints and adducted at the shoulder—all evidence of hyperactivity of ventrally innervated muscles which have developed on the ventral aspect of the limb.

The extension of the fingers at the interphalangeal joints by the interossei is of ventral origin and may be spoken of as ventral extension in order to make clear not only the functions of the muscles concerned ("extension") but also their innervation and their embryology ("ventral"). Thus it is seen that the entire reaction of the upper extremities is but a manifestation of an imbalance between the activation of ventral and dorsal muscles in which the ventral group dominates the picture.

### B. The Head

When both arms are affected the head is flexed and a certain degree of flexion appears in the upper portions of the trunk, based upon a close

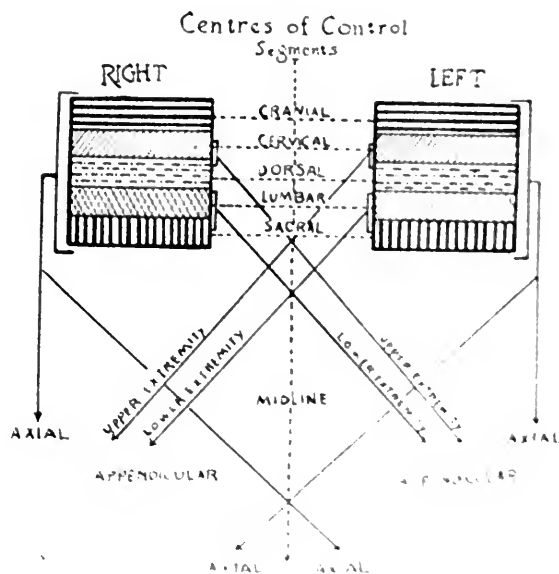


FIG. 1

anatomical relationship of the centres of control of the muscles of the upper trunk and arms. In the re-representation at higher levels of the seg-

mental relations in the spinal cord, the same topographical relations must obtain (Fig. 1). It is but natural therefore, that, when both arms become affected the upper portions of the trunk should also be involved.

The diagram (Fig. 1) illustrates a center controlling ventral and dorsal movements. This diagram represents the right extremity, for example, innervated by one side only of the nervous system, while the same side innervates both halves of the axial musculature. A lesion may affect the centers of one side without affecting the axial musculature, since this is also supplied by the other side. The moment, however, that the lesion becomes bilateral, both unilaterally innervated arms and the innervation of the axial muscles become affected, thus producing the bending or flexion of the head and trunk. This diagram illustrates not only how asymmetrical types occur but also the basis for the common cranio-cervico-brachial types involving the head, neck and arms and the relatively rare lumbosacral types involving the lower extremities.

### C. The Trunk and Leg

In strictly unilateral Parkinsonian syndromes the patient maintains a normally erect position. Neither the hip nor the trunk are flexed. As soon as the disease becomes bilateral, flexion appears, first of the head. It may spread to the trunk and hips. Flexion of the head and of the main part of the trunk is obviously due to a relative over-activity of the ventral musculature as compared to that of the dorsal. It is more difficult to explain flexion at the hip. This move-

ment is carried out mainly by the dorsal ileopsoas, sartorius and tensor fasciae latae and may be called dorsal flexion. However, the condition in unilateral syndromes throws light upon this. In these cases there is no flexion at the hip. The dorsal flexor group is not active. If it were affected and were the cause of the flexion at the hip, it would be involved in the unilateral types, since its innervation is unilateral like that of the appendicular musculature of which it forms a part, and not bilateral as is that of the axial musculature. From this it may be seen that the movement of flexion at the hip has not been brought about by the dorsal ileopsoas, sartorius and tensor fasciae latae but is due to the activity of ventral trunk muscles.

The flexion at the knee is a compensatory response to the pushing forward of the center of gravity, brought about by the overactivity of the ventral trunk muscles.

When the Parkinsonian walks or runs he shows a more or less pronounced tendency to rise upon his toes, which is a manifestation of overactivity of the ventral muscles in the back of the calf.

### D. Cases Showing Asymmetrical Involvement

In this group of cases in which the involvement is more extensive on one side of the brain than on the other, the notion that the postural defect of Parkinson's disease is due to an imbalance of ventral and dorsal muscles in which the ventral group dominates, is very clearly emphasized. Figures 2, 3 and 4 represent two different types of Parkinsonian syndrome. The first two are

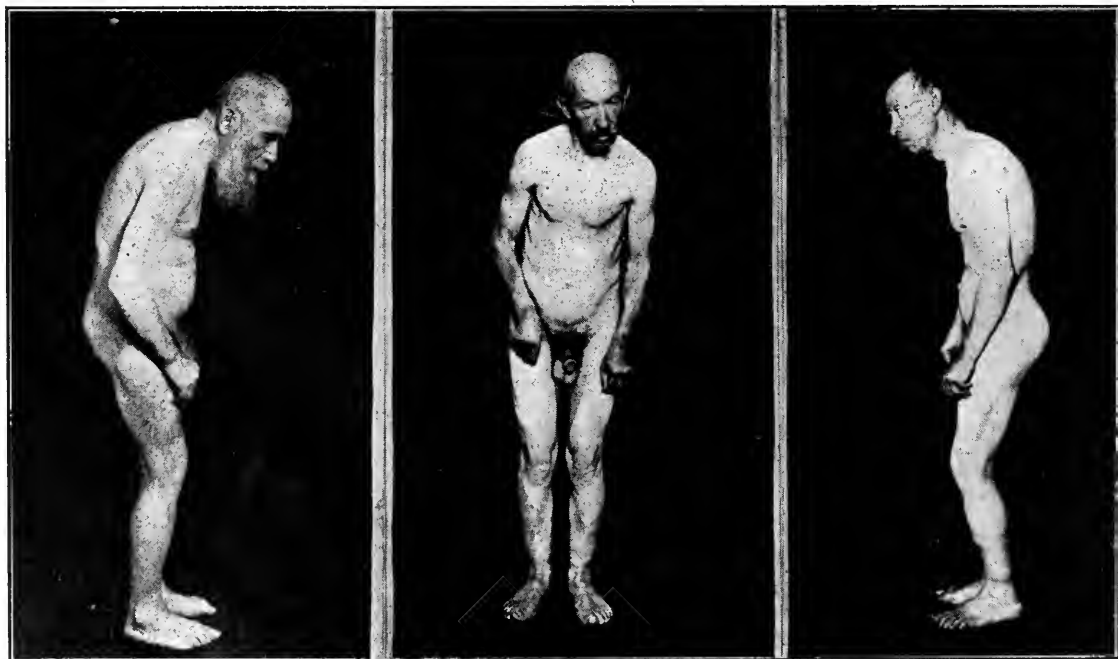


FIG. 2

FIG. 3—Note the greater involvement of the right sterno-kleido-mastoid and of the muscles of the right arm.

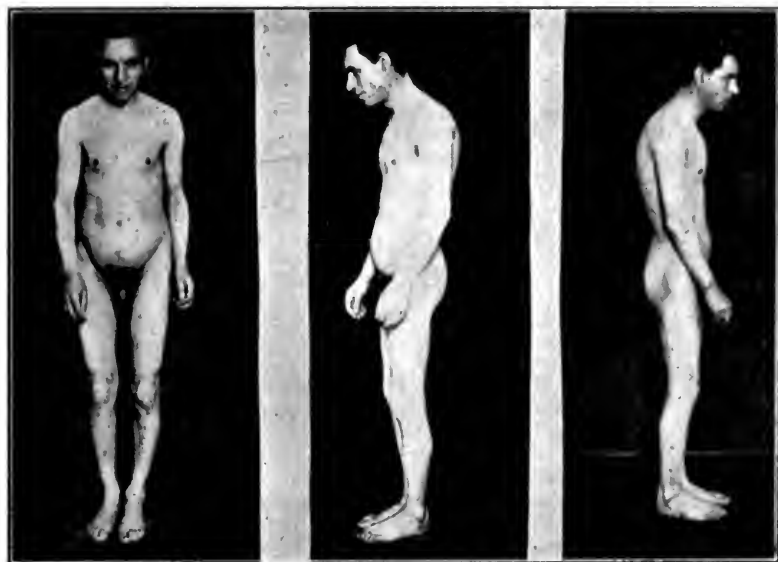


FIG. 4—Note the greater involvement of the right arm.

due to arteriosclerosis, the last due to epidemic encephalitis. In figure 3 a greater involvement on the right side is clearly seen in the arm, in which flexion at the elbow and fingers is more pronounced. The front view indicates also that the right sterno-kleido-mastoid is more active than the left, which brings the head around from the mid-position. The sterno-kleido-mastoid is a ventral muscle. In Figure 4 it will be seen from the front view that the right arm is more affected than the left. The comparison of the positions of the right and left hand in the lateral views emphasizes this difference. In asymmetric cases therefore, the side showing the greater involvement shows a greater activity of ventral muscles. A few words will suffice to indicate that the pes equinus and flexion of the toes, as well as the occasional varus, present like the other positions of the Parkinsonian syndrome, one due to over-

activity of ventral muscles. All of the intrinsic muscles of the foot are like those of the hand ventral. The carrying down of the foot is due to the action of the ventral gastrocnemii and solens.

It is therefore apparent that the posture of a Parkinsonian syndrome represents an imbalance in the innervation of some or all of the groups of muscles of the trunk and extremities, from which there results a pattern indicative of an overactivity of the ventral group.

The involvement is, of course, not always complete either on one side or symmetrical or complete on both sides, depending upon the extent of actual anatomical involvement. Since the re-representation at higher levels

must be similar to that of the segmental arrangements of the spinal cord, it is but natural that in the vast majority of cases, adjacent centers, such as the head and upper extremities, will be simultaneously involved.

## II. CONTRACTURES IN THE PARKINSONIAN SYNDROME

The occurrence of contractures in the Parkinsonian syndrome is rare. They are more rare in the vascular type of the disease than in those following epidemic encephalitis. Dejerine states



FIG. 5



FIG. 5



FIG. 5

"this abnormality of the foot in Parkinson's disease (which to my knowledge has not been reported) is very rare and I have up to now, observed only two cases."<sup>3</sup> Though I have seen many cases of the Parkinsonian syndrome I recall seeing but three showing contracture of the feet, when the cause of the disease was other than epidemic encephalitis. Figure 5 shows a very severe contracture. These contractures are due to overactivity of ventral muscles and form additional evidence of the thesis put forward in this article. The rarity of contractures indicates that disease of some region other than that causing the usual picture of the Parkinsonian syndrome has appeared.

### III. CONCLUSIONS

1. The defects in posture and the contractures of the Parkinsonian syndrome indicate an im-

balance between the activities of certain ventral and dorsal muscles. As a result of this imbalance the activity of certain ventral muscles becomes greater than that of certain dorsal muscles.

2. Normal or, better, increased tone, is required to make this imbalance manifest.

3. The defects of posture and of tone are separate and distinct and are not due to disorder of a single physiological system.

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NOTE: I wish to express my thanks to Drs. S. P. Goodhart and Foster Kennedy for permission to use photographs of cases on their respective services.



# Dystonia Musculorum Deformans

WITH ESPECIAL REFERENCE TO A MYOSTATIC FORM AND THE  
OCCURRENCE OF DECEREBRATE RIGIDITY PHENOMENA.

A STUDY OF SIX CASES

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Dystonia musculorum deformans is not an uncommon disorder. It is well known for its kinetic phenomena, and most, if not all, of the case reports consist of analysis of the peculiar movements which characterize the clinical syndrome. Thus far spontaneous abnormal involuntary movements, torsion spasms, disturbances in tonus and possibly a racial peculiarity have come to be looked on as the criteria for the diagnosis of the bizarre entity. This clinical conception of the disorder, originally formulated by Ziehen and Oppenheim and so closely followed by subsequent observers, stresses only the hyperkinetic phenomena. But we have found cases in which these phenomena are present only to a slight extent or almost entirely absent, and yet we believe that they form part of the disease.

It is the object in this paper, besides recording six hitherto unreported cases of dystonia musculorum deformans with atypical and unusual features, to call attention to the existence of a myostatic variant of the disorder. But far from attempting to create a new clinical entity, we wish to correlate it with the well-known syndrome. This myostatic or postural variant is indeed a part of the disorder and always coexists with the kinetic disturbance of which it is only a complement. It is, in other words, a fleeting postural phase, observed between the waves of movement, become permanent. The occurrence of large and small fragments of decerebrate rigidity in typical cases of dystonia, to which we wish to call especial attention, further emphasizes the postural or myostatic disturbance in the condition. But, whereas in most cases the kinetic disturbance obscures or overshadows the postural element, there are some in which the latter is plainly evident and a few others in which it is dominant to such an extent that

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\* From the Neurological Service of the Montefiore Hospital, New York.

\* Read at the Forty-Eighth Annual Meeting of the American Neurological Association, Washington, D. C., May, 1922.

one begins to doubt whether the pictures are part of the same syndrome. It is our conviction that they are. The following case reports and their discussion will illustrate these points.

#### REPORT OF CASES

CASE 1.—*A case of dystonia musculorum deformans of the kinetic type beginning in the right hand and, up to the present, involving the musculature of both upper extremities, neck and head, with a fragment of decerebrate rigidity phenomena.*



Fig. 1.—A case of dystonia illustrating segmental involvement and a fragment of decerebrate rigidity limited to the right upper extremity.

*History.*—B. M., a boy, aged 15 years, born in the United States, a Jew of Russian parentage, about three and one-half years ago (1918) noticed difficulty in using his right hand, especially in writing. Soon after it was observed that his left upper extremity was held in a peculiar position, namely, flexed at the shoulder and elbow and adducted. About eighteen months after the onset, the patient's head and body began to bend over to the left side. During the course of his illness there gradually developed peculiar defensive movements of his left upper extremity, uncontrollable movements of the head and turning movements of his body.

*Physical Examination.*—The gait was normal. There was a marked involuntary torsion spasm involving the musculature of the head, neck, chest and left upper extremity. The head was rotated and markedly tilted to the left, the chin almost resting on the left shoulder. On extending the right upper extremity, the hand was turned with the palm outward, that is, overpronated, and the index finger was hyperextended. This constitutes a fragment of decerebrate rigidity, the so-called pronator sign of Wilson (Fig. 1). There was a coarse rhythmic tremor of the extended hand. While these movements appeared to come on in rhythmic waves, they were practically continuous in one part or another.

The spontaneous movements of the left upper extremity consisted of protraction of the arm together with flexion of the forearm; this movement was very similar to that assumed in defending one's face. In the upper extremities the dystonic spasm was revealed in an alternating hypertonia and hypotonia. It is curious to note that walking on all fours was accomplished much better than the motor disturbances of the upper extremities would seem to permit. Further neurologic examination was negative.

*Discussion.*—The disease began in one upper extremity, which is rather unusual. Other writers, especially Hunt,<sup>1</sup> have called attention to the frequency with which the disease begins in the lower extremity. This patient also shows an exquisite fragment of decerebrate rigidity in the right upper extremity, although the picture is mainly of the myokinetic variety. Finally, the movements are thus far limited to the head and neck, upper extremities and upper part of the trunk. It is quite possible, in view of the comparatively short duration of the illness, that it will extend downward and involve the rest of the trunk and lower extremities; but for the present the disease has assumed a segmental character. Attention is called to this distribution because a segmental delimitation has previously been pointed out in striatal diseases, especially in paralysis agitans.

*CASE 2.*—*A case of dystonia musculorum deformans of the kinetic type with the occurrence of both fragmentary and almost complete decerebrate rigidity phenomena.*

*History.*—J. L., a boy, aged 11 years, born in the United States, a Jew of Russian parentage, whose parents were first cousins, and who had three other children living and well, had had the disease for three years. It was noted that his left foot gradually began to "turn in" involuntarily when he walked; this became progressively more marked, and one year later his right foot also began to "turn in and to drop." In July, 1921, in the course of two days, there developed frequent spasmodic contractions in the left lower extremity, which made sitting difficult. The spasms steadily increased in severity and frequency. In September, 1921, the patient developed severe spasms in his hands. In August, 1921, walking became impossible on account of the muscular spasms and fatigability. In December, 1921, sitting became impossible, and the patient became bedridden. For the last two months the patient has been lying on his left side with the head turned to the left. Frequent spasms in the left upper extremity and the muscles of the back have also developed. For the last two months the right lower extremity has been held almost constantly in the extended position.

1. Hunt, J. Ramsay: The Progressive Torsion Spasm of Childhood, *J. A. M. A.* **67**:1430 (Nov. 11) 1916.

*Physical Examination.*—The patient was unable to walk or stand. The position of election was the reclining one, with the body inclined to the left and the head bent forward and to the left. The left knee joint was in flexion, the right in extension. Both feet were in hyperplantar flexion, the right more



Fig. 2.—Almost total decerebrate posture in a case of dystonia musculorum.

so than the left. Occasionally the left upper extremity was extended with the palm turned outward. The movements came on in wavelike fashion and seemed to be induced by slight stimulation, such as stroking or pinching the skin. He frequently assumed an attitude of opisthotonos with the right lower

extremity markedly extended and the back in extreme lordosis. The abductors of the thigh, flexors of the leg and to a slight extent the adductors of the right thigh, were in almost constant tonic contraction.

If the boy was suspended by his upper extremities, he assumed a position typical of decerebrate rigidity: the forearms were extended on the arms, the fingers somewhat flexed at the proximal metacarpophalangeal joints, the forearm rotated outwardly (pronator sign), the lower extremities hyperextended and the back lordosed, forming an opisthotonic arc. However, the head was not retracted but hung limply forward with the chin pointing to the left (Fig. 2). There were no movements in the face or head musculature; the sternomastoids occasionally manifested mild tonic contraction. While there was no true pelvic distortion, there was a tendency to torsion toward the left. The erector spinae groups were in a state of constant contraction and occasionally the muscles of the back of the neck participated in the spasm. The muscles were in hypertonic contraction, but this could be overcome by passive movement, even to the point of hypotonia. Both the fingers and the hands

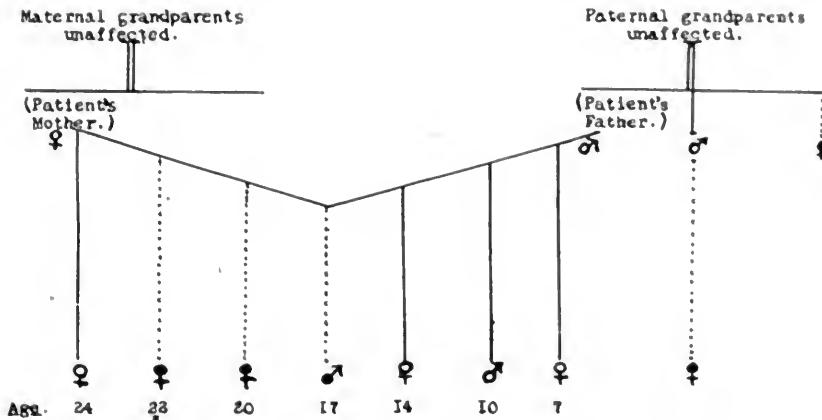


Fig. 3.—Familial incidence of dystonia musculorum deformans in Case 3. The black symbols indicate those affected with the disease. \* indicates the patient.

were definitely hypotonic. There was no adiadokokinesis, no ataxia or dysmetria.

The deep reflexes were difficult to elicit. The abdominal and cremasteric reflexes were present. There were no sensory changes. The cranial nerves were normal, except for the existence of a true nystagmus on extreme gaze to the left.

*Discussion.*—The history of the development, the age of onset, the race of the patient and the abnormal involuntary movements stamp the case as a typical dystonia musculorum deformans, in spite of the fact that there is as yet no torsion of the pelvis. The unusual features are the postural decerebrate rigidity phases. Even as he lies on his back there are rhythmic waves of movement. (We have observed this rhythm in some of the other cases, and it is described in most of those reported in the literature.) The spasms throw the right lower extremity in extension and both uppers in extension, pronation and outward rotation. These movements represent momentary

phases of decerebrate rigidity phenomena. When the boy is suspended, all four extremities and the body assume the typical attitude which occurs on experimental section of the midbrain, with the exception of the position of the head. The occurrence of this phenomenon points to the anatomic delimitation of the lesion in dystonia, even if it does not strictly localize it.

CASE 3.—*An unusual case of dystonia musculorum deformans with (1) a remarkable familial incidence, (2) speech disturbance, (3) a remission of the hyperkinetic phenomena with a resultant (4) myostatic residuum, (5) a hemidystonic distribution, and (6) a fragment of decerebrate rigidity.*

*History.*—L. P., a woman, 21 years of age, born in the United States, was a Jewess of Russian parentage. A remarkable familial tendency to the disease was noted (Fig. 3). The illness began at the age of 12. Her gait became "dragging" and difficult. Later her upper extremities became involved. There was no history of precedent acute infection. The physical examination recorded by Dr. I. Abrahamson on April 5, 1920, revealed a bedridden patient with a typical dystonia with severe involvement of the body, head and neck and all extremities. The speech was dysarthric, bulbar in nature. In January, 1921, improvement was noted. The patient was quieter and able to take a few steps without support. In August, 1921, it was noted that the left hand still showed the rhythmic clonic movements, but there was a tendency to extension and pronation (fragment of decerebrate rigidity). The patient was able to walk fairly well. General dystonic movements were still in evidence. In February, 1922, there was marked remission of all movements with considerable general improvement (Fig. 4). She showed some dystonic movements in the left upper extremity with the rhythmic flexor-extensor movement of the hand at the wrist. The left foot was in equinovarus contracture and also exhibited movements, resulting in a left hemidystonia. The trunk and right side disclosed no movements but assumed the postural condition momentarily observed in the dystonias during the brief interval between the waves of movement; that is to say, that which is the fleeting static element in the kinetic disturbance has become a permanent postural attitude in this patient's remission.

*Discussion.*—In this patient, the onset of whose dystonia dates back to childhood, the condition began in the lower extremities and became progressively worse, until she exhibited a violent form of the typical kinetic disturbance. Added to that she showed a rare involvement of speech (bulbar dysarthria). So far as we are aware, only two other cases referred to in the literature reveal this disturbance (those of St. Bernstein<sup>2</sup> and Wimmer<sup>3</sup>). After two years, during which she became bedridden, a gradual remission set in. It may be of interest to mention that in August, 1920, she had a streptococcus sore throat, and in April, 1921, an acute follicular tonsillitis. One may speculate on the possible bearing of these infections on the remission. The quite remarkable familial history is also worthy of emphasis, in view of the familial tendency of some of the other striatal syndromes, especially since recent criticism tends toward the grouping of numerous clinical entities of a supposedly common basal ganglion origin. Further, although only few dystonic elements are left, they are practically limited to one side—hemidystonia. But

2. St. Bernstein: Ein Fall von Torsions Krampf, Wien. klin. Wchnschr. **25**: 1567, 1912.

3. Wimmer, A.: Etudes sur le syndrome extra-pyramidaux. Spasme de torsion progressif infantile (syndrome de corps strie), Rev. neurol. **28**:952 (Sept.-Oct.) 1921.



the striking feature of this residual state is the static or postural attitude, an attitude to which we also wish to direct attention in some of the succeeding cases and which we designate the myostatic variant, or counterpart, of the myokinetic syndrome.



Fig. 4.—Formerly a kinetic type of dystonia, now a myostatic variant exhibiting a hemidecerebrate posture.

*CASE 4.—A case of dystonia musculorum deformans, illustrating the myostatic or postural form, with few hyperkinetic phenomena.*

*History.*—P. T., a man, aged 20 years, born in Russia, a Jew of Russian parentage, whose illness began in 1913, at the age of 11, one year prior to

the onset fell from a height of about 12 feet, alighted on his feet but sustained no injury. One year later there developed a "drop foot" on the right side, associated with a turning outward of the lower extremity on walking. Three years later his hand began to turn outward, and he found difficulty in using it. About three years thereafter the left lower extremity became affected. The condition has remained stationary to the present day.

*Physical Examination.*—The patient walked with a peculiar gait, in which there was considerable twisting of the pelvis; the vertebral column was thrown forward, producing a marked lordosis; the lower extremities were rotated outward (everted) and in progression the trunk was bent forward and the lower extremities were flung about awkwardly in movements of hyperextension and hyperflexion (Fig. 5). A tendency to hyperadduction produced a scissor-gait effect. The abnormal movements and position of the spine and pelvis largely disappeared when the patient crept "on all fours." Despite the dystonic gait and the tortipelvis, the patient was remarkably free from tonic spasms when at rest. Except for an occasional tremor of the right upper extremity and clonic plantar flexion movements of both feet, there was a paucity of abnormal involuntary movements. There was no play of hypertonia and hypotonia in the affected muscles. A slight degree of hypotonia was present at the wrists.

The patient complained a good deal of various symptoms, was introspective, egocentric and was likely to use high sounding phrases. His attitude at times strongly suggested the functional.

*Discussion.*—The lack of progression, the atypical bizarre gait and attitude, the want of dystonic movements at rest, together with the patient's psychic make-up, speak in favor of a hysterical condition. But further study of the case convinces one of its organic nature and its relationship to dystonia musculorum deformans. For this patient shows the very postural or myostatic phase which may be momentarily observed in all the typical forms of the kinetic syndrome. But, whereas the postural static component is masked by the hyperkinetic phenomena in the general run of cases, in the present instance it has become the dominant feature. Corroborative evidence of the relationship of this syndrome to dystonia musculorum deformans may be found in the history of its development, the age and race of the patient, the torsion-posture of the pelvis, the lordosis, the clonic movements in the feet and the general attitude. The fact that the static phase is partially present in an undoubted case of dystonia musculorum deformans gives weight to the view that where the entire clinical syndrome is dominated by the postural component we are merely confronted with the complementary side of the same picture.

CASE 5.\*—*A postural or static instance of dystonia musculorum deformans (dysbasia lordotica progressiva) with slight kinetic involvement.*

*History.*—H. R., a man, aged 32, a driver, born in Russia, a Jew of Russian parentage, four months after a fall began to feel "stiffness and pulling sensation" in the hamstring muscles of the left thigh, followed by a "drawing sensation" in the left arm and forearm, with a tendency to flexion at the elbow and fingers. At the same time the left side of his face became involved in a similar muscular spasm. In 1912, a laminectomy (seventh cervical nerve to fifth dorsal vertebra) was performed, apparently in the belief that some cord involvement was the cause of his motor disturbance. Prior to the laminectomy alcohol was injected into the left elbow region and left popliteal space, appar-

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\* Opportunity to study this case was afforded through the courtesy of Dr. M. Grossman.

ently with the unfulfilled hope of controlling the abnormal involuntary movements. Both of these operative attempts have left behind physical signs which are independent of the actual condition, yet serve to mask it.

As this case presents almost in its entirety the myostatic variant of *dysbasia lordotica progressiva* and may arouse doubt as to its proper classification in the group of dystonias, it may be mentioned that Drs. I. Abrahamson and J. Ramsay Hunt independently diagnosed the case (1919) as one of dystonia.

*Physical Examination.*—The patient was examined in February, 1922. There was frequent play of the muscles of the face, particularly of the upper lip, resembling a slow grimace. There was a slight tilt of the head and overaction of the *platysma myoides*. The right *sternocleidomastoid* was somewhat more



Fig. 5.—The lordotic attitude in a myostatic form of dystonia.

prominent than the left. There were few or no bodily movements with the exception of some in the toes, which appeared to be a cross between a dystonia and athetosis. On attempting to walk the movements of the toes gained in amplitude. On the right there was dorsal extension of the big toe and fanning of the others when the patient lifted his foot from the floor; this movement was of a dystonic type. There was a slow turning of both feet, especially of the right, into an equinovarus position. The lower extremities were held mainly in an extended position: the feet especially in plantar flexion. The right big toe was frequently held in spontaneous dorsal hyperextension. On suspending the patient by the arms both lower extremities were hyperextended at all joints.

The gait simulated a spastic walk with bilateral dropped foot. It was slow, wide, swinging and shuffling with a broad base, and appeared somewhat inco-

ordinate (Fig. 6). Yet there were no equilibratory and no deep sensory disturbances. The left abdominal reflexes were diminished, the lower deep reflexes increased. There was no true Babinski sign, but there were a left Mendel-Bechterew and a Rossolimo sign. There was neither hypertonia nor hypotonia in the right upper and lower extremities. A slight hypotonia was



Fig. 6.—A typical instance of the myostatic variant of dystonia musculorum. Note the spontaneous Babinski sign and the grimacing facial expression somewhat like that seen in progressive lenticular degeneration (Wilson's disease).

noted in the left lower extremity. There was flexor contracture of the fingers of the left hand into the palm. The left interossei were atrophied. Marked hypertonia was found in the left upper extremity, which was held flexed at an angle of 90 degrees at the elbow. The speech sounded as though the words were uttered through articulated teeth and partly closed lips. The labials

were especially interfered with because of the overaction of the lower facial muscles and platysma. The face appeared spastic, as if a smile were frozen on it.

*Discussion.*—There are a few physical findings in this case which complicate the picture, but it appears that they have been brought about by surgical interference and therefore do not form part of the syndrome. The contracture of the left hand, the atrophied interossei and the fixed hypertonic attitude of the left upper extremity are due to the therapeutic attempts which were made to control the abnormal movements. But the general posture and the few abnormal involuntary movements leave no doubt that the patient represents the myostatic variant of the hyperkinetic syndrome. His gait especially resembles to a marked degree that of the patients in Cases 3 and 4, and indeed that of every case of dystonia if one could subtract the abnormal movements. Additional corroborative evidence that the case belongs to the myostatic form may be found in the fact that the lower extremities assumed the hyperextended decerebrate postural attitude when the patient was suspended in the air with support under the axillae.

The speech disturbance was not of a dystonic character, but resembled more that encountered in progressive lenticular degeneration (Wilson's disease). This may be of some significance in linking together the two syndromes. The spontaneous dorsal extension of the big toe, while not a true Babinski sign, is worth remarking, and will be further alluded to in the next case.

*CASE 6.\*—A case of dystonia musculorum deformans of the kinetic type revealing (1) fragments of decerebrate rigidity, (2) a paralysis agitans-like tremor of right thumb and hand, (3) a dorsal extension (Babinski) of the left big toe.*

*History.*—E. H., a young woman, aged 19, born in the United States, a Jewess of Russian parentage, had had a tenotomy of the left Achilles tendon in 1918. The illness set in gradually at the age of 8, first in the right foot and then in the right hand and upper extremity; later in the right foot; and finally the left upper extremity became affected.

*Physical Examination.*—The gait appeared somewhat spastic. She walked on the toes of the right foot and on the outer margin of the left sole. Both feet were inverted, the left more than the right. The right lower extremity tended to cross in front of the left. While sitting there were observed involuntary inversion of the left foot and occasional extension of both legs on the thighs. Now and then a spontaneous dorsal extension of the left big toe occurred. On extending the arms forward and above the head, the right underwent alternating supination and pronation with a tendency to eversion of the palm.

There were involuntary flexion and extension movements at the right elbow. At times there were small oscillations of the right thumb and hand in a manner closely simulating the tremor of paralysis agitans. The movements in the left upper extremity were much less marked. At times there was over-extension of the left wrist and involuntary flexion of the fingers, together with flexion and extension at the left elbow. There were no involuntary movements of the head and neck and no torsion of the back or pelvis.

The reflexes of the upper extremities could not be elicited owing to the presence of the constant involuntary movements. The knee and Achilles' tendon reflexes were present and equally active. The abdominal reflexes were present and equal. On plantar stimulation there was marked dorsal extension of the left big toe and fanning of the others. This seemed to be an actual reflex response.

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\* For permission to publish this case we are indebted to Dr. Robert E. Pou of the Neurological Institute, New York.

although a spontaneous dystonic Babinski movement also occurred. The cranial nerves were normal except for a slight bilateral horizontal nystagmus.

*Discussion.*—The following facts are worthy of note: First, the restriction of the kinetic disorder to the extremities, giving an appendicular distribution. This emphasizes once more the possibility of the segmental involvement in the disorder, a point alluded to in connection with Case 1. Second, the presence of fragments of decerebrate rigidity in the right upper extremity and in the feet discloses the static component. Third, the paralysis-agitans-like tremor of the right thumb and hand is of particular significance, as it indicates a probable involvement of the efferent pallidal mechanism of the corpus striatum. The presence of this tremor may furnish another clue to the localization of the lesion. Fourth, attention should be directed to the presence of the Babinski toe phenomenon, which is even more marked in this man than in the preceding case.

#### SUMMARY AND DISCUSSION

The six cases summarized in this paper show a number of features which hitherto have not been associated with dystonia musculorum deformans. It is quite difficult to explain the nystagmus in three of the cases, unless it is assumed that the ocular movements are part of the dystonia. Although this is somewhat far-fetched, it may be pointed out that irregular movements of the eyeballs have been observed in violent choreas. So, too, it is difficult to interpret the presence of the Babinski sign in Case 6 without other signs of involvement of the pyramidal tract. Further, the fanning of the lesser toes and the dorsal extension of the big toe is occasionally observed in the same patient during the spontaneous movements. Case 5 also exhibits this spontaneous dorsal extension and fanning. One is tempted to speculate on the significance of the Babinski phenomenon and to question whether it is really primarily a pyramidal tract phenomenon or an unexplained striatal release mechanism.

The speech disturbances in two of the cases are also unusual. Two other cases reported in the literature showed similar disturbances. Wimmer's recent report mentions difficulty in speaking, but the statement is made that this was not a dysarthria. The speech was explosive; there was poverty of words and sometimes echolalia. There is no reason why the speech muscles should not be involved in dystonia in view of their undoubted striatal and cerebellar innervation. In this connection one may again instance chorea in which dysarthria is not uncommon. If an attempt is made to correlate dystonia with lenticular degeneration, it is not surprising that there is speech disturbance, although this is of quite a different type in the latter disease. The speech disturbance in Case 5 was somewhat reminiscent of Wilson's syndrome.

In many of the cases which we have described, and in numerous others reported, there is something wavelike or rhythmical to the movements. Rhythm in general is such a universal phenomenon and

in animal movement so primitive that special emphasis should be given to its presence in dystonia. Very likely it represents a reversion to a lower segmental characteristic of movement. In this connection it may be once more pointed out that two of the cases showed an actual tendency to segmental distribution of the affection.

The racial element, which, though very common, is not universal, was found in all of our patients. So, too, there was an apparent yet noteworthy functional tinge to some of the cases. It is well known that many of the patients in the early stages of the disease are considered hysterical. Case 1 bore the burden of that diagnosis for one year and Case 4 is still reminiscent of it, and yet there is no doubt as to the organic nature of the condition. Wilson's illuminating remarks on decerebrate fragments in hysteria may serve as possible explanations in this connection.

We called attention to the occurrence of decerebrate rigidity phenomena in the cases herein recorded. Wilson<sup>4</sup> made passing mention of them in dystonia, but he did not follow up his observations. His allusion, however, suggests a static component in the hyperkinetic disorder. The importance of the demonstration of this combination, as well as the dissociation, lies in the fact that it furnishes clinical evidence for the accepted notion of the physiologic unity of posture and movement. Conversely, there is sufficient physiologic evidence to support the view that there does exist a closely interwoven static counterpart of the kinetic form of the disease. The conception of movement as recently elaborated by numerous observers<sup>5</sup> permits the inclusion in one entity and proves the basic relationship of two apparently dissimilar clinical pictures, namely, the myostatic and the myokinetic variants of dystonia.

This enlarged conception is not altogether novel, at least from the point of view of correlating several clinical entities which are probably based on one anatomic substratum. Strümpell originally postulated an amyostatic syndrome in which he included Westphall's pseudo-sclerosis, Wilson's lenticular degeneration and paralysis agitans. At the same time that a special attempt was made to define the clinical syndromes of dystonia lenticularis (Thomalla) and double athetosis, attention was called to their common underlying physiologic mechanism and anatomico-pathologic substratum. The conviction has gradually arisen that the numerous clinical entities are not quite so capable of sharp delimitation as was originally thought. Attention was even drawn to the fact that disease of the liver may occur not alone with

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4. Wilson, S. A. K.: On Decerebrate Rigidity in Man and the Occurrence of Tonic Fits, *Brain* **43**:220, 1920.

5. Goodhart and Tilney: Brady Kinetic Analysis of Somatic Motor Disturbances, *Neurol Bull.* **3**:295 (Sept.-Oct.) 1921.

lenticular degeneration but with dystonia musculorum deformans as well, thus showing that they are related in another way. Further, it was shown that far from being limited to the corpus striatum, the lesion in dystonia may be very diffuse. A recent review of the clinical syndromes of the corpus striatum by Lhermitte<sup>6</sup> lent but little clarity to the situation and only served to show that the same kinetic disturbance may be due to different lesions and that the same lesions may give rise to different kinetic disturbances. In other words, in the present state of our knowledge, it is futile to attempt too sharp a definition of the clinical or pathologic syndromes.

As few cases of dystonia have come to necropsy, Wimmer's fairly typical case may be cited in connection with the rather universal tendency to consider the disease one of basal ganglion, more especially lenticular, origin. On microscopic study Wimmer found cellular degeneration and neuroglial changes in the caudate and lenticular (putamen) nuclei, in the dentate nucleus of the cerebellum, in the thalamus, pons and cerebral cortex. The changes simulated those seen in pseudosclerosis and those found in the striatum were not more marked than elsewhere. Wimmer further quotes Spielmeyer to the effect that one might regard Wilson's lenticular degeneration, pseudosclerosis and torsion spasm as "variations in clinical expression of a pathologic process which is essentially the same."

Hall<sup>7</sup> has also pointed out that the pathologic process is not limited to the lenticular nucleus, but involves the pons and cerebral cortex as well. He further states that degeneration of the liver may be found alike in progressive lenticular degeneration, pseudosclerosis and dystonia musculorum deformans. Schneider<sup>8</sup> adds that hepatic cirrhosis may be found in dystonia lenticularis as well as in the syndromes just mentioned. In Wimmer's case, too, the liver was cirrhotic.

It may be of interest to point out that the syndrome under discussion is termed either *dysbasia lordotica progressiva* or *dystonia musculorum deformans*. There is no question that they are one and the same clinical entity. And yet one name stresses the peculiar postural attitude in the gait and the other emphasizes the abnormal movements. The important fact is that these two phases have been noted, although they have not been correlated.

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6. Lhermitte, J.: The Anatomical and Clinical Syndromes of the Corpus Striatum, *Neurol. Bull.* **3**:163 (May) 1921. Translated from the *Annales de Medicine* of August, 1920, by Huddleston and Kraus.

7. Hall, H. C. (of Copenhagen): *La Dégénérescence Hepato-lenticulaire*, Paris, 1921.

8. Schneider, Erich: *Torsionspasmus: ein Symptomkomplex der mit Leberzirrhose verbundenen progressiver Lenticulardegeneration*, *abstr., Neurol. Zentralblatt* **39**: (April) 1920.

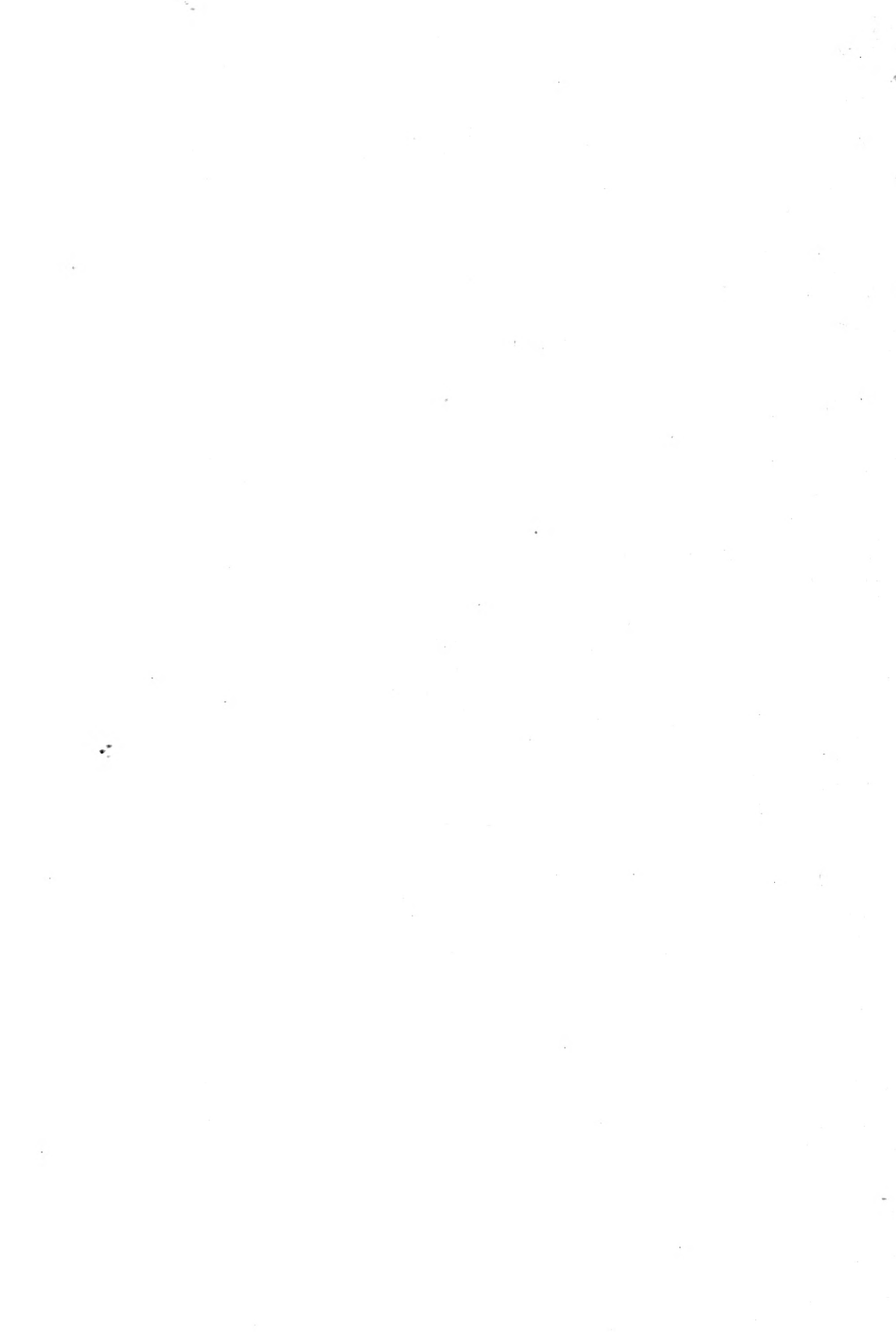


The occurrence of a parkinsonian tremor in a true case of dystonia (Case 6) may serve as a further link in the chain of striatal syndromes. Paralysis agitans may be used by way of analogy to show that it is quite possible for either a kinetic or static phase to dominate a clinical picture. Just as there are cases of paralysis agitans which are characterized by tremor and others by the loss of associated movements and postural attitudes, so there are cases of dystonia which are made prominent by the abnormal movements and others which are signalized by the postural attitude.

#### CONCLUSIONS

1. There exists a myostatic variety of dystonia musculorum deformans as contrasted with the usual myokinetic form.
2. Phenomena of decerebrate rigidity may frequently be observed in dystonia musculorum deformans.
3. All cases of dystonia have an underlying postural background, one of the manifestations of which are the phenomena of decerebrate rigidity.
4. The myostatic and myokinetic phases of dystonia, which may be observed in all cases, are capable of dissociation. Either the static or kinetic phase may dominate the clinical picture.
5. The involvement in dystonia may be segmental in character.
6. In dystonia there occur not infrequently signs of other striatal diseases which point to a common anatomic and physiologic relationship.

We wish to express our thanks to Dr. A. M. Rabiner, resident neurologist of the Montefiore Hospital, for his kind assistance in obtaining the photographs of the patients.







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## Original Papers.

### ON THE PRODUCTION OF NEUROMUSCULAR PATTERNS BY RELEASE OF SPINAL INTEGRATIONS AFTER DECEREBRATION.\*

BY WALTER M. KRAUS AND  
ABRAHAM M. RABINER, NEW YORK.

- I.—INTRODUCTION.
- II.—THE NEUROMUSCULAR MECHANISM.
- III.—A NEUROMUSCULAR ANALYSIS OF THE EXPERIMENTAL AND CLINICAL EVIDENCE FOR DECEREBRATE RIGIDITY AND THE FLEXION REFLEX.
  - A. The Experimental Evidence.
  - B. The Clinical Evidence for Decerebrate Rigidity.
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  - D. Summary.
- IV.—CASE REPORTS.
- V.—THE FLEXION REFLEX POSITION OF THE ARM.
- VI.—THE RELATION OF POSTURE PATTERNS TO TONE.
- VII.—THE KINETIC AND STATIC TYPES.
- VIII.—SUMMARY AND CONCLUSIONS.

#### I.—INTRODUCTION.

THANKS to the efforts of S. A. K. Wilson, we now have a clinical application of that part of the experimental work of Sherrington which demonstrated the existence, after removal of the more anterior parts of the central nervous system, of the condition known as decerebrate rigidity. This clinical and pathological study promises to clear up many of the obscure problems, not only of defects of posture, but of the physiology of the nervous system in general. It

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\* From the Neurological Department of the Montefiore Hospital, New York.

is our desire to assist in this by analyzing, from a new angle, a series of cases showing decerebrate posture.

One of us<sup>1</sup> in November, 1921, presented a preliminary general outline of this new approach to the subject of motility and posture. In this paper decerebrate postures will be considered from that point of view.

## II.—THE NEUROMUSCULAR MECHANISM.

The essential point of the neuromuscular approach to the subject of motility and posture lies in two assumptions. One is that a description of groups of movements in terms indicating merely the activity of muscles in changing the position of various parts of the body in a geometrical sense has, on careful analysis, no definite relationship to any integration of movements by the spinal cord or higher centres of the nervous system. The other assumption is that movements, grouped or isolated, must be considered as activated by the nervous system in patterns primarily dependent upon the primitive and anatomical grouping of muscles, and not upon their function only. The peripheral motor neurones and their end-organs, the muscles, have group relations indicating integration by the spinal cord. This implies that the anatomical grouping of muscles, the common nerve-supply of certain groups of them, their common origin on certain aspects of the body, must form bases for the interpretation of group movements. The simplest example of this is the division of the musculature of the back, neck, and abdominal wall into dorsal and ventrolateral groups. The application of this information to physiology reveals immediately that the dorsal group causes extension while the ventrolateral group causes flexion. The lateral and rotatory movements produced by these groups of muscles are due to over-activity of the right or left halves of either the dorsal or ventral groups or both.

In the more distant portions of the extremities the muscles also develop in large 'premuscle masses' from the ventral and dorsal aspects.<sup>2</sup> These masses give rise to groups of muscles whose nerve-supply are respectively dorsal and ventral. For example, of the branches of the brachial plexus going to the arm, forearm, and hand, the circumflex and musculospiral are dorsal, and innervate muscles derived from the dorsal premuscle mass, while the musculocutaneous, median, and ulnar are ventral, and supply muscles derived from the ventral premuscle mass (*see Table IV*). However, an examination of the functions of muscles does not always reveal a correspondence between actual function and that expected. In other words, muscles developing on the dorsal aspect of the limb have not always dorsal functions, such as extension, and vice versa. The best examples of

this are as follows : The muscles iliopsoas, pectineus, sartorius, on the anterior aspect of the thigh, since they are dorsal in origin (part of the so-called femoral group), would, by analogy with the axial muscles, be expected to have an extensor function, whereas, in reality, their function is flexor. In the hand the interossei extend the terminal phalanges, though, with the exception of the abductor digiti quinti, all the other muscles supplied by the ulnar nerve and of the same group have a flexor function. Since the actual anatomical facts form the basis of the entire matter, these must be presented at once. In *Tables I, II, and III* the muscles of the body, except those supplied by cranial nerves, will be found arranged in dorsal and ventral groups. In *Table IV* the spinal motor nerves will be found so arranged. This last tabulation has been taken from Patterson's article in Cunningham's *Text-book of Anatomy*.<sup>3</sup>

*Table I.*—DIVISION OF THE MUSCLES OF THE UPPER EXTREMITY INTO VENTRAL AND DORSAL GROUPS.

MUSCLE	VENTRAL	DORSAL
1.—Levator scapulae		✓
2.—Serratus anterior		×
3.—Rhomboides major		×
4.—Rhomboides minor		×
5.—Supraspinatus		×
6.—Infraspinatus		×
7.—Teres minor		×
8.—Deltoid		×
9.—Subscapularis		×
10.—Teres major		×
11.—Latissimus dorsi		×
12.—Subclavius	×	
13.—Pectoralis major	×	
14.—Pectoralis minor	×	
15.—Biceps brachii	×	
16.—Brachialis*	×	
17.—Coracobrachialis	×	
18.—Brachioradialis		×
19.—Extensor carpi radialis longus		×
20.—Extensor carpi radialis brevis		×
21.—Supinator		×
22.—Extensor pollicis longus		×
23.—Extensor indicis proprius		×
24.—Abductor pollicis longus		×
25.—Extensor pollicis brevis		×
26.—Extensor communis digitorum		×
27.—Extensor carpi ulnaris		×
28.—Extensor minimi digiti quinti		×
29.—Anconeus		×
30.—Triceps		×

\*Supplied by both dorsal and ventral nerves.

*Table I.*—DIVISION OF THE MUSCLES OF THE UPPER EXTREMITY INTO VENTRAL AND DORSAL GROUPS—*continued.*

MUSCLE	VENTRAL	DORSAL
31.—Pronator teres - - - -	×	
32.—Flexor carpi radialis - - -	×	
33.—Palmaris longus - - - -	×	
34.—Flexor digitorum sublimis -	×	
35.—Flexor digitorum profundus	×	
36.—Flexor pollicis longus - -	×	
37.—Pronator quadratus - - -	×	
38.—Lumbricalis 1 - - - - -	×	
39.—Lumbricalis 2 - - - - -	×	
40.—Lumbricalis 3 - - - - -	×	
41.—Lumbricalis 4 - - - - -	×	
42.—Abductor pollicis brevis -	×	
43.—Opponens pollicis - - - -	×	
44.—Flexor pollicis brevis (lateral head)	×	
45.—Flexor pollicis brevis (medial head)	×	
46.—Flexor carpi ulnaris - - -	×	
47.—Adductor pollicis obliquus -	×	
48.—Adductor pollicis transversus	×	
49.—Interosseus volaris 1 - - -	×	
50.—Interosseus volaris 2 - - -	×	
51.—Interosseus volaris 3 - - -	×	
52.—Interosseus dorsalis 1 - - -	×	
53.—Interosseus dorsalis 2 - - -	×	
54.—Interosseus dorsalis 3 - - -	×	
55.—Interosseus dorsalis 4 - - -	×	
56.—Opponens digiti quinti - - -	×	
57.—Flexor digiti quinti brevis -	×	
58.—Abductor digiti quinti - - -	×	

*Table II.*—DIVISION OF THE MUSCLES OF THE LOWER EXTREMITY INTO VENTRAL AND DORSAL GROUPS.

MUSCLE	VENTRAL	DORSAL
1.—Iliacus - - - - -		×
2.—Psoas major - - - - -		×
3.—Psoas minor - - - - -		×
4.—Pectineus* - - - - -		×
5.—Sartorius - - - - -		×
6.—Rectus femoris - - - - -		×
7.—Vastus lateralis - - - - -		×
8.—Vastus medialis - - - - -		×
9.—Vastus intermedius - - - -		×

\*Supplied by both dorsal and ventral nerves.



Table II.—DIVISION OF THE MUSCLES OF THE LOWER EXTREMITY INTO VENTRAL AND DORSAL GROUPS—*continued*.

MUSCLE	VENTRAL	DORSAL
10.—Tensor fasciæ latæ - - - -		×
11.—Gluteus minimus - - - -		×
12.—Gluteus medius - - - -		×
13.—Piriformis - - - -		×
14.—Gluteus maximus - - - -		×
15.—Biceps femoris (short head) - - - -		×
16.—Biceps femoris (long head) - - - -	×	
17.—Semitendinosus - - - -	×	
18.—Seminembranosus - - - -	×	
19.—Adductor magnus - - - -	×	
20.—Obturator externus - - - -	×	
21.—Adductor longus - - - -	×	
22.—Adductor brevis - - - -	×	
23.—Gracilis - - - -	×	
24.—Obturator internus - - - -	×	
25.—Superior gemellus - - - -	×	
26.—Inferior gemellus - - - -	×	
27.—Quadratus femoris - - - -	×	
28.—Tibialis anterior - - - -		×
29.—Extensor hallucis longus - - - -		×
30.—Extensor digitorum longus - - - -		×
31.—Peroneus tertius - - - -		×
32.—Peroneus longus - - - -		×
33.—Peroneus brevis - - - -		×
34.—Extensor digitorum brevis - - - -		×
35.—Gastrocnemius - - - -	×	
36.—Soleus - - - -	×	
37.—Plantaris - - - -	×	
38.—Popliteus - - - -	×	
39.—Tibialis posterior - - - -	×	
40.—Flexor digitorum longus - - - -	×	
41.—Flexor hallucis longus - - - -	×	
42.—Quadratus plantæ - - - -	×	
43.—Abductor digiti quinti - - - -	×	
44.—Flexor digiti quinti brevis - - - -	×	
45.—Opponens digiti quinti - - - -	×	
46.—Interosseus plantaris 1 - - - -	×	
47.—Interosseus plantaris 2 - - - -	×	
48.—Interosseus plantaris 3 - - - -	×	
49.—Interosseus dorsalis 1 - - - -	×	
50.—Interosseus dorsalis 2 - - - -	×	
51.—Interosseus dorsalis 3 - - - -	×	
52.—Interosseus dorsalis 4 - - - -	×	
53.—Adductor hallucis - - - -	×	
54.—Lumbricalis 1 - - - -	×	
55.—Lumbricalis 2 - - - -	×	
56.—Lumbricalis 3 - - - -	×	
57.—Lumbricalis 4 - - - -	×	
58.—Abductor hallucis - - - -	×	
59.—Flexor digitorum brevis - - - -	×	
60.—Flexor hallucis brevis - - - -	×	

*Table III.*—DIVISION OF THE MUSCLES OF THE AXIS INTO VENTRAL AND DORSAL GROUPS.

MUSCLE	VENTRAL	DORSAL
<b>Muscles of the Back.</b>		
Serratus posterior superior - - -		×
Serratus posterior inferior - - -		×
Splenius - - - - -		×
Sacrospinalis - - - - -		×
Iliocostalis - - - - -		×
Longissimus - - - - -		×
Spinalis dorsi - - - - -		×
Semispinalis - - - - -		×
Multifidus - - - - -		×
Obliquus capitis inferior - - -		×
Obliquus capitis superior - - -		×
Rectus capitis posterior major - -		×
Rectus capitis posterior minor - -		×
Rotatores - - - - -		×
Interspinales - - - - -		×
Intertransversarii - - - - -	×	
Trapezius - - - - -		×
<b>Muscles of the Neck.</b>		
Scalenus anterior - - - - -	×	
Scalenus medius - - - - -	×	
Scalenus posterior - - - - -	×	
Longus capitis - - - - -	×	
Rectus capitis anterior - - - - -	×	
Longus colli - - - - -	×	
Rectus capitis lateralis - - - - -	×	
Sterno-cleido-mastoid - - - - -	×	
<b>Muscles of the Thorax.</b>		
Intercostales - - - - -	×	
Levatores costarum - - - - -	×	
Subcostales - - - - -	×	
Transversus thoracis - - - - -	×	
<b>Muscles of the Abdominal Wall.</b>		
Obliquus externus abdominis - - -	×	
Obliquus internus abdominis - - -	×	
Cremaster - - - - -	×	
Transversus abdominis - - - - -	×	
Pyramidalis abdominis - - - - -	×	
Rectus abdominis - - - - -	×	
Quadratus lumborum - - - - -	×	
<b>Muscles of the Perineum.</b>		
Sphincter ani externus - - - - -	×	
Corrugator cutis ani - - - - -	×	
Transversus perinei superficialis -	×	
Bulbocavernosus - - - - -	×	
Ischio-cavernosus - - - - -	×	
Sphincter urethrae membranacea -	×	
Transversus perinei profundus - -	×	
<b>Muscles of the Pelvis.</b>		
Levator ani - - - - -	×	
Coccygeus - - - - -	×	

*Table IV.*—DIVISION OF THE NERVES OF THE EXTREMITIES INTO DORSAL AND VENTRAL GROUPS.

ORIGIN		NERVES	
<i>Upper Extremity.</i>			
Brachial Plexus.	Dorsal trunks (posterior cord)	(	Dorsal scapular Long thoracic Suprascapular Subscapular (2) Thoraco-dorsal
		(	Axillary Radial
	Ventral trunks (lateral and medial cords)	(	Nerve to subclavius Anterior thoracic (2) Musculocutaneous Median Ulnar
<i>Lower Extremity.</i>			
Lumbo-sacral Plexus.	Dorsal trunks	(	Superior gluteal Inferior gluteal Nerve to piriformis Femoral Peroneal
	Ventral trunks	(	Obturator Nerve to obturator internus and superior gemellus Nerve to quadratus femoris and inferior gemellus Tibial

This division of the nerves and, as naturally would follow, of the muscles of the body, is also to be found in part in Braus,<sup>4</sup> Quain's *Anatomy*,<sup>5</sup> and Lewandowsky.<sup>6</sup> Indeed, the whole general notion of such a division was recognized to a certain extent by Thomas Huxley<sup>7</sup> in 1871, in his description of the surfaces of the limbs and their axial borders. Since the functions of these muscles, particularly those of the limbs, are familiar to all, they have not been included in the tables. The difference between an expected function in terms of the dorsal or ventral origin of a given muscle and its real function has been emphasized briefly by citing the femoral group and the dorsal interossei. When this same critical examination of the correspondence between function and origin of muscles is applied to the hamstrings, for example, it is found that whereas they flex at the knee, they also extend at the hip—a curious combination. When the movements at the ankle are considered, it is found that the gastrocnemius and soleus group, though posteriorly placed in the leg, and though developing from what is really its ventral aspect,

have a dorsal function, extension. They are innervated by a ventral nerve which also innervates the flexors of the toes and the intrinsic flexors of the foot. The confusion which has resulted from this alone is tremendous. The attempts to reconcile function on one hand, with anatomy, embryology, and nerve-supply on the other, have led to insurmountable difficulties so far as any satisfactory solution is concerned. However, when in addition to actual movements of muscles, we consider their embryological grouping and their nerve supply, we find that all of these difficulties disappear.

In order to keep in mind this division of muscles, it is proposed that the words 'ventrad' and 'dorsad' be added when necessary to our present terminology to indicate the control and origin of muscle movements such as extension, flexion, abduction, etc.; the suffix 'ad' instead of 'al' is thus used to indicate that primitively these muscles produced movements to and from the ventral surfaces of the body. To be sure, all movements are not primarily such, but a group of movements such as flexion, internal rotation, adduction, and inversion obviously have the same general effect, while the movements of extension, abduction, external rotation, and eversion have the opposite effect.

In another paper<sup>8</sup> emphasis is laid upon the fact that the movements of the leg in normal gait can be resolved into four phases: (1) A ventral fin-like movement at the hip; (2) A dorsal fin-like movement at the hip; (3) The flexion reflex element; (4) The support element.

The first two of these represent movements of the extremities of a vertebrate with but singly-hinged appendages, namely fins. When, in the course of vertebrate evolution, fish developed into land animals, amphibia, and acquired three-hinged appendages, more complex movements were necessary. The three-hinged appendage had not only to be locked in extension to counteract gravity, but had also to be withdrawn from the ground. Land animals therefore developed a more complicated integration of the nervous system to control this. These two latter sets of movements, which are corresponding opposites, include the two last elements of gait, those of flexion and support, and it is these which are made manifest in an uncontrolled fashion by the process of decerebration, either experimentally in animals or by disease in man.

The position of antigravity posture as defined by Sherrington<sup>9, 10</sup> is spoken of as 'extension', while the flexion reflex element is spoken of as 'flexion'. The impression given, therefore, is that these two sets of movements are physiologically homogeneous, and the implication is that the nervous system bears a similar relation in controlling them. However, in the following it will be shown that both the

extension and flexion alluded to consist of an alternation of ventral and dorsal movements, not a simple and homogeneous reaction. These reflexes of posture and progression are, of course, guided by integrations of the spinal cord. Their make-up is obviously more complex than one which would only guide the movements of a large ventral or dorsal group of muscles in a concerted fashion. The postural reaction of the trunk of the body in opisthotonus illustrates by way of contrast a simple over-activity of the dorsal group in relation to the ventral group.

### III.—A NEUROMUSCULAR ANALYSIS OF THE EXPERIMENTAL AND CLINICAL EVIDENCE FOR DECEREBRATE RIGIDITY AND FLEXION REFLEX.

*A. The Experimental Evidence.*—In a paper entitled "The Reflex Mechanism of the Step", Sherrington<sup>9</sup> has given the actual

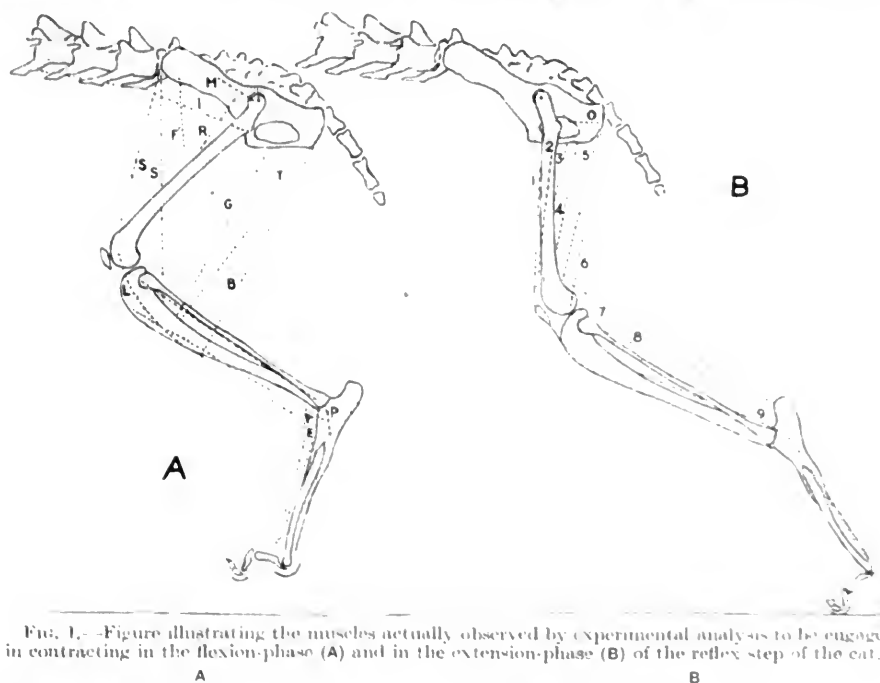


FIG. 1.—Figure illustrating the muscles actually observed by experimental analysis to be engaged in contracting in the flexion-phase (A) and in the extension-phase (B) of the reflex step of the cat.

- A. Tibialis anticus.  
B. Biceps femoris posterior.  
E. Extensor brevis digitorum.  
F. Tensor fasciæ femoris brevis.  
G. Gracilis.  
I. Psoas.  
L. Extensor longus digitorum.  
M. Gluteus minimus.  
P. Peroneus longus.  
R. Rectus femoris.  
S. Sartorius lateralis.  
S'. Sartorius medialis.  
T. Semitendinosus.

1. Quadratus femoris.  
2. Crureus.  
3. Vasti.  
4. Adductor minor.  
5. Adductor major (a part).  
6. Semimembranosus.  
7. Biceps femoris posterior.  
8. Gastrocnemius.  
9. Soleus.  
10. Flexor longus digitorum.

*Table V.*—THE ABOVE MUSCLES ARRANGED IN VENTRAL AND DORSAL GROUPS.

*Note.*—In both tables *Group I* includes muscles acting at the hip, *Group II* those acting at the knee, *Group III* those acting at the ankle. *Fl.* = Flexion; *Ext.* = Extension; *Ad.* = Adduction.

GROUP	A		B	
	VENTRAL	DORSAL	VENTRAL	DORSAL
I.		I. Psoas M. Gluteus minimus R. Rectus femoris F. Tensor fasciæ femoris brevis S. Sartorius lateralis S'. Sartorius medialis	0. Quadratus femoris 3. Adductor minor 4. Adductor major (a part) 5. Semimembranosus 6. Biceps femoris posterior	
II	B. Biceps femoris posterior G. Gracilis T. Semitendinosus			1. Crureus 2. Vasti
III.		A. Tibialis anticus L. Extensor longus digitorum P. Peroneus longus E. Extensor digitorum brevis	7. Gastrocnemius 8. Soleus 9. Flexor longus digitorum	

## THE CORRESPONDING MUSCLES IN MAN.\*

I	Pectineus (Fl. & Ad. hip)	Iliopsoas (Fl. hip) Tensor fasciæ femoris (Fl. hip) Sartorius (Fl. hip) Pectineus (Fl. hip)	Adductors (Ad. hip) Semimembranosus (Ext. hip) Semitendinosus (Ext. hip) Biceps femoris (Ext. hip)	
II	Gracilis (Fl. & Ad. knee) Semitendinosus (Fl. knee) Semimembranosus (Fl. knee) Biceps femoris (Fl. knee)			Quadriceps femoris (Ext. knee)
III		Tibialis anticus (Fl. ankle) Extensor digitorum longus (Fl. ankle) Extensor longus hallucis (Fl. ankle)	Gastrocnemius (Ext. ankle) Soleus (Ext. ankle) Tibialis posticus (Ext. ankle)	

\*This does not account for all the muscles of the lower extremities, since observation or testing of all of them has not been possible.

muscles involved in the extension or antigravity phase of reflex stepping and in the flexion phase in the cat. *Fig. 1* represents the results<sup>9</sup>; following this is a table (*Table V*) showing the division of muscles into dorsal and ventral groups, and below this, for convenience and future use, the corresponding muscles in man.

From this it is readily seen that there is a definite alternation of control at the three great joints, the hip, knee, and ankle.

Furthermore, in speaking of the muscles of the axis, Sherrington<sup>9</sup> states that "when all of the brain in front of a transection between

anterior and posterior colliculi is removed in a cat or dog, the decerebrate preparation thus obtained exhibits a systemic postural reflex with the following features . . . the dorsal muscles of the back, neck, and tail, the retractors of the head, and the elevators of the lower jaw, are all in harmoniously co-ordinated steady tonic contraction."

From this it may be seen that the muscles of the extremities show an alternation from axis towards periphery at the knee and hip respectively, and, in addition, this alternation is carried on in the axial muscles in which the dorsal group is over-active. The formula, therefore, for the limbs in decerebrate rigidity, going distally, is VDV, and the formula for the limbs and axial musculature, the axial being most proximal, is DVDV. These letters refer respectively to axis, hip, knee, and ankle. This experimental evidence is clearly cut, and forms the basis of a conception of muscular pattern in decerebrate states, to be illustrated later by case reports. Experimentally this pattern is more clearly defined than would be expected in the less uniform effects of human pathological processes.

**B. The Clinical Evidence for Decerebrate Rigidity.**—The first clinical description of decerebrate rigidity was given by S. A. K. Wilson<sup>11</sup> in November, 1920, a quarter of a century after the first experimental description by Sherrington. Wilson showed that a great variety of disorders, such as cerebral abscesses and tumours, cerebellar tumours, intraventricular haemorrhage, acute purulent meningitis and ependymitis, tuberculous meningitis, hydrocephalus, congenital diplegias, chorea, athetosis, and dystonia lenticularis, could cause a picture resembling this or fragments thereof. A few quotations from his paper will suffice to give the movements affected.

*Case 1* (p. 223).—"The arms were extended by the sides, slightly flexed at the wrists and notably rigid. The legs were also extended and adducted, with toes pointed down and in."

"11.45 p.m. About this time both arms became rigid, the left rather more than the right. Both were adducted at the shoulder and strongly extended at the elbow, with pronounced internal rotation and hyperpronation; the wrists were flexed, so that the palms of the hands looked up and out, quite turned away from the body." (*Fig. 2.*)

"1.25 a.m.—When the patient was seen again, after about an hour's interval, he was in the same extensor position, arms adducted at shoulders, extended at elbow, flexed at wrist, whole arm rotated inwards and hyperpronated: on the right the thumb was between the first and second fingers of the hand, but not on the left. The legs were rigidly extended, feet inverted, great toes dorsiflexed."

*Case 2* (p. 227).—"The whole of the musculature of trunk, arms and legs became rigid; the arms and legs were extended to the fullest extent, the arms by the sides and pronated, while the hands were clenched and wrists slightly flexed. The legs were slightly inverted, the feet more notably so, with the toes pointing down and in."

*Case 3* (p. 228).—"The upper extremities were adducted and internally rotated, the forearms strongly hyperpronated, so that the backs of the hands faced each other; trunk and neck were extremely rigid and the latter slightly retracted; the legs were similarly in full extension, heels drawn up, toes pointing down and feet inverted."

*Case 4* (pp. 229 and 231).—"A brief period of excitement and moaning ushered in the attacks, which consisted of sudden powerful opisthotonus and head retraction, the neck straightening and the occiput nearly touching the shoulders. The left arm relinquished its flexed attitude and became strongly extended, the forearm over-pronated, the wrist extended and the third and fourth fingers flexed, while the thumb was flexed into the palm. The legs were in fullest extension with heels up and toes down, and the right arm was as the left, except that it was rather less inverted and the hand was in the form of a fist. Trunk and limbs alike were absolutely rigid."

*Case 5* (p. 231).—"March 6, 1906: The legs were now extended again, and so were the arms. The patient lay unconscious, with the arms extended by the sides and the forearms notably hyperpronated. The hands were clenched. The legs were also fully extended, with feet inverted and toes pointing down and in."



FIG. 2.—The typical decerebrate attitude of extension pronation.  
(By kind permission of 'Brain'.)

*Case 6* (p. 233).—"The arms were fully extended, adducted, strongly hyperpronated; the backs of the hands faced each other, and at the same time the wrist and finger flexors were conspicuously contracted; the neck was stiff from muscular rigidity, but was not retracted in any degree; the lower extremities were in full extension and adduction, with heels drawn up, toes pointing down, and feet slightly inverted."

*Case 7* (p. 235).—"His arms went out in front of him, extended and hyperpronated, with hands clenched and wrists flexed."

When these descriptions are compared with the tables of movement given by Sherrington and with *Tables I, II, III, IV, and V*, it will be seen that the formula D—axis, V—shoulder and hip, D—elbow and knee, and V—wrist and ankle and below, is clearly present.

The quotations from Wilson's paper were chosen to illustrate clearly-defined patterns. Many of his descriptions, as would be expected from the character of the pathological process, were not so



precise. The lack of clearly defined pattern in many cases appears to us susceptible of easy interpretation, as indeed has been suggested by Wilson. In the cases which follow we have fortunately been able to find a precise formula in all but one. In the light of the neuromuscular approach, these formulæ become significantly indicative of curious and inexplicable patterns in other conditions.

**C. The Clinical Evidence for the Flexion Reflex.**—When the illustrations from Sherrington's article on "The Reflex Mechanism of the Step"<sup>9</sup> are examined, it is seen that the flexor phase, or the flexion reflex element, forms a corresponding opposite to the anti-gravity position. "A complete flexion reflex consists of a single flexion at the hip and knee, with dorsiflexion of foot and toes."<sup>12</sup>

Reference to the tables added to these illustrations shows that the formula is D—hip, V—knee, D—ankle for the limbs, going distally, in contrast to the VDV of antigravity posture. Furthermore, it has been shown by Walshe,<sup>12</sup> Riddoch,<sup>13</sup> and others that a well-marked contraction of the abdominal musculature occurs with the fully-developed flexion reflex. Therefore the formula becomes VDVD for the musculature of the limbs and trunk, and is in contrast to the DVDV formula of antigravity posture. These letters refer respectively to the axis, hip, knee, and ankle. *Case 5* described below (*Fig. 9*) illustrates this.

**D. Summary.**—From this it may be seen that, not only in decerebrate posture, but also in the corresponding opposite, the flexion reflex, an alternating formula exists in the extremities, which is not unexpected, after all, when one considers the optimum mechanical needs of appendages consisting essentially of three segments which must be folded up and extended. This alternation is also present when the axial musculature is included.

#### IV.—CASE REPORTS.

In the case reports given below, not only movements as such, but the rôle of individual muscles in causing these movements, have been repeatedly and most carefully observed. The axial movements, and all movements of the extremities, except those at the shoulder, are easy to analyze by observation and various clinical tests. Certain difficulties appear at the shoulder, due to the fact that both dorsal and ventral muscles bring about the same movement, notably internal rotation. These muscles are the pectorals of the ventral group, and the latissimus dorsi, subscapularis, and teres major of the dorsal group. However, it is very easy to palpate both the pectorals and the latissimus, and thus determine which of these large muscles is in action.

*Case 1.—R. E. (Fig. 3).*

**History.**—In October, 1919, at the age of 15, the patient was taken with a respiratory disorder manifesting itself as a cold and bronchitis, unassociated with expectoration. She complained of pain in the chest. She was treated at various hospitals and dispensaries. The respiratory symptoms cleared up, but the pain remained for almost a year, until Sept. 25, 1920. At that time she had been suffering from excessive drowsiness for a month. She complained of diplopia, headache, fever, drooping of the right eyelid, and dragging of the left foot. At Christmas, 1920, choreiform movements in the legs began which prevented her from sitting still. Two days later similar movements appeared in both hands, and, two days after that, in the neck and head. By this time the diplopia had disappeared, though



FIG. 3.—Note the adduction at the shoulders, the decerebrate position of the left arm, and the adduction at the hips.

ptosis and dragging of the left foot still persisted. On Jan. 21, 1920, she was admitted to Bellevue Hospital, where she remained for five months. Three months after admission the ptosis disappeared. While at Bellevue the movements were those seen in the kinetic form of decerebrate posture. A precise analysis of the muscles involved was not made at that time. It was noted then that the functional element was large. The underlying process, however, was felt to be epidemic encephalitis. After discharge from Bellevue and a brief stay at the Metropolitan Hospital, she was admitted to Montefiore Hospital, Sept. 29, 1921.

**Physical Examination.**—At the present time examination shows bilateral ptosis, nystagmoid oscillation in the lateral plane, and weakness of the lower facial muscles on the right. Standing unassisted is impossible. There is no other involvement of the muscles supplied by the cranial nerves except the spinal accessory, which will be described under axial musculature.

**Axis.**—There is definite arching of the body with retraction of the head, simulating typical opisthotonus. She has shrugging movements of the shoulder which are produced by the action of the trapezius. The

sterno-cleido-mastoid on the right contracts occasionally.

**Upper Extremities.**—The arms are adducted and rotated inwardly, and the pectorals can be felt to contract when this movement occurs. There is no contraction of the latissimus, the deltoids, rhomboids, or spinati muscles. The forearm is extended on the arm by the triceps, and the wrist is pronated and flexed. While at Bellevue it was noted that the fingers were consistently flexed and adducted during the movements, while here the first finger is extended. The present finger movements imitate classical athetosis.

**Lower Extremities.**—In the lower extremities there is a constant movement of what appears, on first analysis, to be flexion, and what really is a spasmodic adduction, of the thighs due to definite contraction of the adductors. Occasional contraction of the pectineus is felt (supplied by both

dorsal and ventral nerves). When the legs are abducted there are active adductor movements which bring the legs to the mid-line. During this movement flexion at the hip does not occur. The iliopsoas, sartorius, tensor fasciae latae, and glutei do not contract. When the patient is on her abdomen and the knee is flexed at right angles, rhythmic extension movements produced by the quadriceps occur. When she is on her back the hamstrings can be felt to contract. This does not produce flexion at the knee, but rather slight extension at the hip. Rhythmic movements accentuate a rather mild equinovarus position. The toes are flexed in this movement.

*Summary.*—Of the muscles which could be tested, the following are found active and producing movements:—

1. AXIAL

Extensors of the head, neck, and back

Trapezius

Right sterno-cleido-mastoid

2. APPENDICULAR

*a. Upper extremity*

1. Shoulder Pectorals

2. Elbow Triceps

3. Wrist Flexor group

Pronators

4. Fingers Long flexors

Extensor indicis proprius

Adductor and flexors of the thumb

Volar interossei and lumbricales

*b. Lower extremity*

1. Hip Pectineus

Hamstrings

Adductors

2. Knee Quadriceps

3. Ankle Gastrocnemius

Soleus

Tibialis posterior

4. Foot Long and short flexors

Abductors

With the exception of the sterno-cleido-mastoid, only dorsal axial muscles come into play. Movements at the shoulder and hip are brought about by ventral muscles, those at the elbow and knee by dorsal muscles, those at the wrist and ankle by ventral muscles. In the fingers and toes the movements are ventral except that of the extensor proprius.

*Diagnosis.*—Epidemic encephalitis, choreic and kinetic type.

*Case 2.*—L. R., age 13 (*Figs. 4 and 5*).

*History.*—The patient was admitted to the Montefiore Hospital on April 8, 1922. The history obtained from the mother was that the child had not been well for about two years. She was irritable as a rule, easily disturbed, and fainted frequently. The mother believes she may have been feverish at times. There is no history of diplopia (?). In February, 1922, she was brought home because movements of the limbs, head, and trunk had begun. After staying a month in another hospital she was admitted to Montefiore Hospital.

*Physical Examination.*—On first sight she presents the picture of chorea. The arms, legs, and head are moving almost continually. The

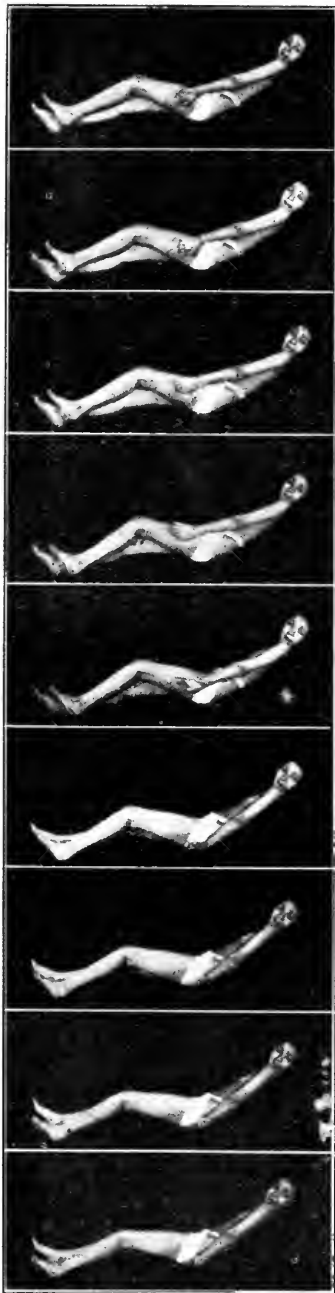


FIG. 4.—This series (reading downward) shows the arm passing from a decerebrate position (adduction of the shoulder, extension at the elbow, hyperpronation at the wrist) to one of rest. The left leg passes from adduction to rest at the same time.

duration of the movement is less than a second when timed by a stop-watch. More careful observation shows that certain definite groups of muscles are brought into activity, thus producing a continual repetition of the same postural patterns. When the patient is asleep there are no abnormal positions or postures. With the exception of the movements noted, the physical examination is quite negative. The cranial muscles are negative except for those supplied by the spinal accessory, which will be mentioned below.

*Axis.*—The extensors and rotators of the head bring about retraction and rotation. Slight opisthotonic movements are occasionally noted. When the patient is more excited, these movements become more pronounced. The trapezius and sterno-cleido-mastoid are occasionally contracted on both sides. With the exception of this latter muscle, no activity of the ventral muscles of the axis has been noted.

*Upper Extremities.*—When the patient is relatively quiet, the pectoral group at the shoulder adducts and internally rotates the entire arm. As the series of moving pictures shows (Fig. 4), this movement alternates with one of rest. At the elbow the triceps extends the arms. At the wrist the flexors are in action as well as the pronators. The flexors of the fingers and thumb, as the photograph (Fig. 5) and moving picture show, are also in action.

It may be seen from this that there is an alternation of activity of ventral and dorsal muscles, the formula of which is at the shoulder ventral, at the elbow dorsal, at the wrist and below ventral.

*Lower Extremities.*—The legs are carried forward and across the mid-line by the ventral adductor group. The iliopsoas is not in action, as can be plainly made out on examination. When the legs are widely spread, flexion at the hip is not seen; instead, the legs are adducted. Extension at the hip by the hamstrings is also present. The gluteal group of muscles is not in action except when the axial muscles are bringing about opisthotonus. At the knee the hamstrings produce no flexion; on the contrary, the dorsal quadriceps group extends. At the ankle the gastrocnemius and soleus and tibialis posterior produce extension, and the

flexors of the toes are active. As reference to *Table III* will show, this last is entirely a ventral action.

The formula for the leg is therefore identical with that of the arm—at the hip ventral, at the knee dorsal, at the ankle and below ventral. When the patient's movements become excessive owing to excitement, the pattern ceases to be so precise, and other muscles begin to contract. These muscles are the antagonists of those noted above. This is a relatively rare occurrence.

*Summary.*—The patient shows activity of the dorsal musculature of the trunk, and an alternating formula for the extremities. The only exception is the sterno-cleido-mastoid. Occasionally the antagonists of these muscles go into action.

*Diagnosis.*—Epidemic encephalitis, choreic and kinetic type.



FIG. 5.—Note the right arm and the adduction of the right leg. Compare with Fig. 2.

*Case 3.*—J. S., age 17 (*Figs. 6 and 7*).

*History.*—This patient was admitted to the Montefiore Hospital on May 1, 1922. She has had a rather stormy career, but despite family opposition had worked hard in pursuing her studies at high school. She graduated in January, 1920. She then studied at a business school, graduating at the head of her class. She began stenography, and since has done exceptionally well.

Between January and July, 1920, she began to feel tired and sleepy during the day, and restless at night. She could not sleep well. In July, 1920, she went to the country, but did not improve, and so returned home after two weeks. In August, 1920, she had pains in her legs, with fever, lasting one week. In January, 1921, there occurred a family quarrel centred about a sexual affair, and followed by a disturbed night. In the morning she noticed movements of the hands, feet, and head. She could not talk. Some improvement occurred, but two days later diplopia and fever were present. She soon became delirious, and was admitted to the Lenox Hill Hospital, where she stayed three months. After a stay in the country her general condition improved. In May, 1921, after an attack of vomiting associated with abdominal pain, she was admitted to Bellevue. Following this her movements were intensified, and she was admitted to the Neurological Institute, where she remained nine weeks. There was considerable improvement, but she continued to attend the dispensary until February, 1922. In March, 1922, she entered Mt. Sinai with abdominal pain and depression. She became very noisy and excited, and was occasionally confused, especially at night. She finally left the hospital and was admitted to Montefiore Hospital May 13, 1922.

**Physical Examination.**—On first observation the patient's condition suggests chorea. The extremities and head are moving continually. These movements are not so pronounced when she is calm and unobserved. The emotional reaction resultant upon examination intensifies the movements. Careful observation shows that the activity of certain groups of muscles predominates and produces a repetition of the same postural pattern.

**Cranial Nerves.**—When the patient is quiet, the motor cranial nerves are also at rest. When excited, there is frequent grimacing, the tongue is protruded straight forward and to the right and left.

**Axis (Fig. 6).**—There are opisthotonic movements. The head is pulled backward, the spine is curved. The patient states that sometimes



FIG. 6.—Note the opisthotonic movement in particular.



FIG. 7.—Note the positions of the arms, hands, and feet.

this begins at the neck and passes wave-like to the end of the body. At other times either the neck region or the lumbar region is alone affected. The trapezius is found active on both sides, but more so on the right. It elevates the shoulder at times. The sterno-cleido-mastoid on the right is sometimes in action, though rarely. The lower ventral trunk muscles (abdominals) occasionally contract, but never bring the body forward.

**Upper Extremities.**—Some of the shoulder muscles are active. The scapula is moved out and up. On analysis this is found due to the trapezius and to internal rotation by the pectorals. The deltoids and rhomboids are never in action. Occasionally a contraction of the latissimus dorsi is observed. The triceps is almost always contracted, the elbow flexors are rarely so. Flexion occurs at the wrist, though extension is also observed at times. Pronation is frequently noted, but supination also

occurs, though less often. When extension is present supination is noted also. The fingers do not show as typical or as constant a response as that which occurs in *Cases 1 and 2*.

*Lower Extremities.*—The dorsal muscles at the hip do not take part in any of the movements. The patient states that her leg is never carried forward, either when standing or in bed. None of the following muscles contract in any of the movements: iliacus, psoas major and minor, pectineus, sartorius, and tensor fasciae latae. The glutei do not contract while standing or when on the abdomen or back. The adductors are powerfully active, and may be felt when prone, supine, or standing. This movement appears one of flexion, but is not in the dorsoventral plane but at an angle tilted towards the mid-line. When the patient is on her abdomen, extension at the hip is produced by the hamstrings, while the glutei are definitely relaxed. The patient states that her leg is twisted inwards (inwardly rotated). She does not confuse this with inversion of the foot. The leg is continually held in extension, and never when standing or prone goes into flexion. The feet are inverted, the right one more so than the left, and extended so that the dorsum of the foot is almost in a straight line with the long axis of the tibia. When standing, both feet are inverted, the right much more than the left. When walking, the external lateral border of the foot is turned to the ground owing to inversion (*Fig. 7*). This can be momentarily overcome, but immediately returns.

*Summary.*—In this case of epidemic encephalitis there is a well-defined picture showing a rhythmic recurrence of opisthotonus and the antigravity posture. When the patient is quiet this is easily made out. When excited there is overflow into the opposite pattern, though even then it occurs much less frequently than that of the antigravity posture.\*

*Diagnosis.*—Epidemic encephalitis, choreic and kinetic type.

*Comments on Cases 1, 2, and 3.*—The diagnosis in the three cases is epidemic encephalitis of the kinetic and choreic types. It is extremely interesting that at one time or another each of these three cases was diagnosed as hysteria. The hysterical element, or what might better be considered functional overflow, is marked. Were it not for the findings in the case of R. E., namely, paresis of one leg, persistent and partial ptosis of both eyelids, diplopia, nystagmus, headache, and fever; for the prolonged illness in L. R., with fever and delirium; and the insomnia, fever, diplopia, and intestinal and bladder disorders in J. S., these three patients could be considered as hysterics. However, it is now well known that the lesions of epidemic encephalitis not only produce pictures which are subject to great exaggeration by mental factors, but that the disease may be practically latent until mental shocks occur. There is no difference, in the effect of physical and psychic trauma in bringing this disease to light, from what familiarly occurs in other diseases of the nervous system, such as paralysis agitans and tabes dorsalis.

\*At the end of August the contractures at the ankles and of the toes had so increased and the movements had become so marked and chaotic as to give the picture of dystonia lenticularis.

*The Muscular Element.*—In all three cases the muscles involved in producing the patterns described were almost identical. Indeed, if it were not for a few exceptions, the descriptions of any one of the three cases would fit the others. In all of them the dorsal axial muscles were instrumental in causing movements. In all of them the muscles described by Sherrington, and then by Wilson, as producing patterns of decerebrate posture, were in action. It is extremely interesting that those muscles which are engaged normally in maintaining an erect posture should appear as clearly as they did. The formula for the arms and legs was, in all three cases, ventral movements at the hip and shoulder, dorsal movements at the knee and elbow, and ventral at the wrist, ankle, and below. In addition, the ventral axial sterno-cleido-mastoid muscle was active in all three cases. We are unable to explain this to our satisfaction, but feel that it may have to do with separate control by the nervous system of cephalo-rotatory movements. Further study of this matter will have to be made.

The alternating formula VDV of the extremities was complicated in *Cases 2* and *3* by the appearance of a reverse formula, DVD. Occasional abduction of the arm and flexion of the elbows was seen (*Cases 2* and *3*). More frequent than this were movements of extension and supination at the wrist (*Case 3*). These movements were carried out by dorsally innervated muscles. Further discussion of this flexion reflex formula in the arm appears in Section V.

The movements of the fingers in L. R. and in R. E. in the earlier periods of their illness were definitely flexor. Later on, some of the finger movements involved extension at the metacarpophalangeal joints. In J. S., movements of extension and flexion were somewhat mixed. That this was not unexpected will be later referred to in Section V, where the finger movements in both the antigravity and flexion reflex arm postures receive more attention.

*Case 4.*—Herbert S., age 28 (*Fig. 8*).

**History.**—The patient, a cutter, was admitted to Montefiore in April, 1921, and died in October, 1921. He was admitted with the following history. Following a 'cold' in October, 1920, which was associated with gastro-intestinal symptoms, there occurred thermo-hypæsthesia in the lower extremities. Both legs below the knees felt cold when taking a warm bath. A week later stiffness of the left leg occurred, and the next morning dribbling of urine. He then entered the Neurological Institute, and after three weeks noticed some improvement. Soon after, fever developed— $101^{\circ}$  to  $104^{\circ}$ —associated with swelling of the left elbow. This lasted three weeks. Following this he was unable to walk or stand, though he could move his feet in bed. At this time the sphincters were more severely involved, with bladder incontinence and retention of feces. Two weeks prior to admission he again had a temperature for two days, and could not move either his arms or his head. This was associated with pain in his left shoulder and side.



**Physical Examination.**—The patient is confined to bed and unable to move unaided. The motor cranial nerves are normal. There was, however, in a previous examination, slight right central facial palsy. The head is rigidly maintained in a normal position when lying down, but when sitting up he can both hold it up and move it in all directions. He is unable to maintain a sitting position by himself, owing to paralysis of the axial musculature.

**Upper Extremities (Fig. 8).**—Voluntary movements in the upper extremities are lost, with the exception of movements which carry the arms from a horizontal position upwards from the bed. Flexion and extension of the fingers of the right hand, and flexion of the fingers in the left hand are also absent. The arms are rigidly extended. The pectoral muscles pull the arms forward to the chest. They are very hypertonic. The arms are held extended on the elbows by the triceps on both sides. On the right the biceps shows normal tone, while on the left it is extremely hypertonic. This does not produce flexion. On the right the forearm is pronated so that the ulnar border of the hand faces directly upward. On the left this pronation is only carried to an angle of  $45^\circ$  to the horizontal plane. On the right the wrist is flexed to a right angle. The fingers are forcibly extended at the two terminal phalangeal joints. When flexed by the examiner they returned to the extended position with an elastic-like bound. The thumb is adducted and slightly flexed at the proximal joint. The fingers are adducted. The left hand is extended at the wrist, nearly at right angles, while the fingers are flexed at the first interphalangeal joint. The gradation of flexion passes from about  $5^\circ$  at the index finger to  $90^\circ$  at the little finger. The thumb is flexed at the proximal joint and adducted into the palm. The position of the left hand is much like that due to the associated movements resultant upon making a fist, that is, flexion at the fingers and extension at the wrist.



FIG. 8.

**Lower Extremities.**—These are both rotated so that the lateral plantar borders of the foot rest upon the bed. They are flaccid, and present only the defects due to loss of tone and voluntary power, notably flexion of the toes and of the sole of the foot, with extension at the ankle (pes cavo-equinus).

**Sensation.**—Lost from the third dorsal segment downward.

*Reflexes.*—The jaw-jerk is extremely lively. The deep reflexes are not obtained in the arm. The abdominal reflexes are absent. The knee-jerks are diminished.

Throughout the examination the patient showed 'flexor spasms' of the legs. The slightest stimulus caused this retraction. It has been necessary to hold the patient's legs down by a sheet to prevent these seizures. Once during the examination, reflex priapism was noted. Control of the bladder is lost.

*Spinal Fluid.*—This shows the following: increased pressure; globulin ++; flocculent precipitate; reduction to Fehling's diminished; cells 70.

*Wassermann.*—Blood and spinal fluid negative; blood culture and spinal fluid negative.

*Urine.*—Negative.

*Summary.*—The patient presented a varying course, and finally died a bulbar death. He ran a septic temperature throughout his stay in the hospital. A diagnosis of severe infective meningo-encephalomyelitis was made. The flaccidity of the legs and the sensory changes from the third dorsal segment downward, coupled with the reflex spasm, reflex priapism, and reflex incontinence, indicated a very severe lesion in the upper dorsal cord. The extremely spastic paralysis of the arm muscles, the transient facial palsy, and rigidity of the neck indicate that the process involved higher portions of the neuraxis.

*Comments.*—We have used this case to illustrate a static hypertonic condition in the upper extremities, showing difference in posture on the two sides. Though the condition of the lower extremities is pertinent to the subject of this paper, we shall leave a discussion of this matter for the next case. The points which we wish to emphasize are that: (1) The state of the upper extremities was unchanged for a considerable length of time. (2) No choreic movements were present. (3) The asymmetry in the two hands, as showing in *Fig. 8*, was very striking. It indicated that the process must have involved slightly different centres as far as the forearm and finger muscles were concerned. On the side in which pronation was most marked, flexion of the wrist was complete. On the side where pronation was relatively slight, extension at the wrist was present. (*See also Section VII.*)

*Case 5.*—Harry S., age 36, metal worker (*Fig. 9*).

*History.*—The patient was admitted Sept. 29, 1921, to Montefiore Hospital, complaining of weakness in both limbs, constipation, and difficulty in passing urine. In August, 1919, he complained of 'stomach trouble', which consisted of pain in the 'stomach' and a feeling of a constricting band around the abdomen. In May, 1921, he noticed pain in the knees, which in a few weeks crept upward to his hips. It was more intense on the left than on the right. This pain remained, and in July he experienced what he describes as a 'freezing sensation and pins and needles' in the soles of his feet. Simultaneously weakness was noticed. A lumbar puncture was done, after which he lost the power of using his legs completely. Urgency of urination appeared, as well as constipation, more marked than before. In the early part of August his legs began to stiffen in extension, and grew progressively worse.

**Physical Examination.**—On admission, the cranial nerves were negative. The deep reflexes in all the extremities were exaggerated. The upper abdominals were present, the left lower easily exhausted and the right not obtainable. There was marked spasticity of the lower extremities. Knee- and Achilles-jerks were hyperactive. There was bilateral ankle-clonus, with a Babinski on the left, questionable on the right. Sensory loss from D7 downward existed. He always lay with the lower extremities in extension until after the operation performed by Charles Elsberg on Nov. 26, 1921. After the operation the abdominal muscles contracted, the thigh was flexed on the hip. The muscles taking part in the contraction were the whole femoral group. The foot was at right angles to the leg (*Fig. 9*), the entire picture representing the flexion reflex described by Walshe<sup>12</sup> or the nociceptive reflex of Sherrington,<sup>9</sup> or paraplegia in flexion described by Babinski. Knee- and ankle-jerks were active.

Part of Elsberg's operative notes follow: An extradural tumor was found lying mostly on the the posterior aspect of the dura and extending



FIG. 9.—Note the position described as 'flexion at the three great joints' or 'paraplegia in flexion'. The formula is: dorsal at the hip, ventral at the knee, and dorsal at the ankle. This ankle position was more conspicuous on examination than is shown here.

beneath the 4th, 5th, 6th, 7th, and 8th dorsal vertebrae. A large amount of it was excised, but fragments remained in various places in front of the dural sac. There was no doubt that there was more tumor below the parts exposed.

**Diagnosis.**—Endothelioma (?).

**Comments.**—This patient showed typical hypertonic paraplegia in extension before operation, and typical hypertonic paraplegia in flexion after it. The increase of tone was as great after the operation as before. *This indicates clearly that tone flexes into pattern.* Pattern changed in this case from that of the antigravity reflex to that of the flexion reflex. The tumour being cervical, it must have damaged the control of lower integrations. This indicates that the pattern of decerebrate posture of the legs must be carried out by

neurones lying within the spinal cord. The presence in the legs of decerebrate rigidity is almost an exact counterpart of an experimentally-produced picture. Why the corresponding opposite pattern developed after operation is not clear. The case illustrates the successive static fixation of two spinal patterns of opposite muscular formula, the first VDV, the second DVD. (*See also* Section VII.)

#### V.—THE FLEXION REFLEX POSITION IN THE ARM.

Up to now emphasis has been laid upon the formula for the legs in the corresponding opposite positions of antigravity posture and the flexion reflex. This has been examined in the light of the experimental work of Sherrington and the clinical work of Wilson and ourselves. For the arms, the formula for the position corresponding to the antigravity position in the legs has been illustrated in the case reports and discussion. However, the position in the arms which would correspond to the flexion reflex element in the leg has not been defined. This, as would be expected, would present a formula opposite to that of the decerebrate arm—notably, dorsal at the shoulder, ventral at the elbow, and dorsal at the wrist. In the course of our investigation of this matter a lengthy paper by Riddoch and Buzzard,<sup>14</sup> which considered this subject, came to our attention. They describe a flexion reflex of the upper limb as follows: "The reflex response, for which the convenient term is 'flexion reflex of the upper limb', was readily obtained in No. 5. On scratching the palm of the paralyzed hand there occurred *flexion of fingers,\** wrist, and elbow, slight abduction and external rotation of the upper arm, and elevation of the shoulder. These were the main components of the general response, which varied in details according to the situation of the stimulus within the receptive field" (p. 434). However, in another place (p. 421), in describing associated movements following stimulation, the effect upon the upper limbs is given as follows: "The upper limbs became rotated outwards at the shoulders, flexed at the elbows, *extended at the wrists with slight supination of the forearms; the fingers became extended at the metacarpophalangeal joints and flexed at the interphalangeal joints, while the thumbs were extended and abducted*".\*

An analysis of this long paper will not be made here. Suffice it to say that, if the formula for the 'extension reflex' or the antigravity posture is VDV, as is indicated clearly by the findings of Wilson, Riddoch and Buzzard, and ourselves, it would be presumed that the corresponding opposite to this would have an opposite

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\* Italics by the authors.

formula and would conform to the movements described in the quotation last given. It would be expected that there would be abduction at the shoulder, flexion at the elbow, extension at the wrist and at the metacarpophalangeal joints. This brings up a matter of considerable importance in the analysis of reflex patterns at the distal joints of the limbs which bears not alone on the question of the upper extremity, but also upon the Babinski reflex and its associated phenomena in the lower extremities. The Babinski phenomena will be given special consideration in another paper.

The intrinsic muscles of the hand are all of ventral origin. Adduction and abduction of the fingers, extension at the phalangeal joints, abduction and adduction of the thumb and little fingers, are all brought about by these ventral muscles. When, therefore, there occurs activation of a pattern which demands a dorsal reaction in the long muscles acting on the wrist and fingers, and when the impulse activating this pattern flows into the intrinsic muscles of the hand, no dorsal intrinsic muscles are there. In the antigravity position the long flexors of the wrist and fingers *and* the intrinsic muscles of the hand are activated (ventral muscles). In the flexion reflex element the long extensors of the wrist and fingers (dorsal) are activated, while the intrinsic hand muscles (ventral) are not. This last produces extension at the wrist, extension at the metacarpophalangeal joints, abduction of the thumb, and, in some instances, extension of the phalanges. Contraction of the extensor digitorum may produce this, depending upon the strength of the stimulus. Consequently the typical picture may include either extension or flexion at the phalangeal joints. The long flexors of the fingers are not active in producing flexion, the volar interossei and lumbricales are opposed by the extensor digitorum communis, the adductor of the thumb by the long abductor.

*The postural pattern of the flexion reflex of the arm consists therefore of dorsal activity at the shoulder, ventral activity at the elbow, and dorsal at the wrist and fingers.*

At the shoulder the large number of dorsal muscles makes it possible to have a number of different reactions. The following from Riddoch and Buzzard<sup>14</sup> indicates the appearance of the reaction which we have just defined, and also the possible variations: "The movement most commonly obtained consists of adduction and external rotation at the shoulder, flexion at the elbow, and extension of the hand and fingers, but the response varies in a remarkable manner with alternation in the locality of the stimulus. Thus, when the reaction is excited by scratching the palm of the hand, the movement at the shoulder is abduction and retraction of the upper arm. Stimulation of the back of the forearm yields adduction at the

shoulder, and of the inner aspect abduction at this joint. Again, when the stimulus is applied to the skin over the deltoid, the response is mainly strong elevation of the shoulder with adduction and external rotation of the upper arm" (pp. 437, 438). This emphasizes the variations found.

The pattern which we have described for the flexion reflex of the arm appeared in *Case 3* (J. S.). It occasionally followed or alternated with the antigravity posture. This represents the alternating stepping movements (reflex walking) produced experimentally by Sherrington. It has also been seen in a man suffering from spastic tetraplegia, shown at autopsy to be due to pressure upon the lower brain-stem of an apricot-sized aneurysm of the right vertebral artery.

In the movements of athetosis, dystonia lenticularis, and chorea, these patterns, often fragmentary, can be made out, as Wilson has emphasized. The positions sometimes change so rapidly that it is only by means of successive cinematographic pictures that the analysis can be made.

## VI.—THE RELATION OF POSTURE PATTERNS TO TONE.

In this paper it is assumed, that not only the integration which produces the flexion reflex, but also that producing the corresponding opposite pattern, notably the pattern of antigravity posture or reflex standing, is entirely spinal. In order to defend this assumption it will be necessary to consider some of the experimental work undertaken in producing decerebrate preparations. Sherrington<sup>9</sup> states: "This reflex standing disappears when the transection of the brain is made behind the posterior edge of the pons", and "the experiments of Horsley<sup>15</sup> and Thiele show that decerebrate rigidity is hardly seriously impaired by successive sections of the cerebellar region until the paracerebellar nuclei are invaded". Wilson,<sup>11</sup> in his paper on decerebrate rigidity in man, states in discussing the pathogenesis of this condition: "In the first place there is general agreement that decerebrate rigidity makes its appearance after transection of the neuraxis at the level of the anterior colliculi, and disappears by a second section below the neuronie level of the medulla". Sherrington<sup>9</sup> has stated: "When in the dog the spinal cord is severed in the thoracic region, the hind-limbs cannot at first stand; but after lapse of weeks or months they exhibit this power. That is, with hind-feet on the ground the reflex tonus of limb-extension suffices to bear the weight of the limbs and superincumbent hind-quarters. The attitude thus exhibited indubitably amounts to standing, and is sometimes maintained for minutes at a time".

It would appear from these four quotations that, in the first place, removal of the central nervous system down to a point "behind

the posterior edge of the pons" still permits the existence of reflex standing or antigravity posture, and the fourth quotation above indicates that this same reflex position may be obtained in an animal whose cord has been transected in the thoracic region. It is furthermore true that *no difference results in the pattern obtained when the brain is transected successively from the anterior colliculi to a "point behind the posterior edge of the pons"*. In other words, no change in pattern is produced by such successive removals of brain tissue. When a section is made below the point at the posterior edge of the pons, or, to use Wilson's words, the "neuronic level of the medulla", the rigidity disappears. But this is due to a transitory loss of tone, as has been suggested by both Sherrington and Wilson, caused by the removal of the grey matter in the regions between the pontine section and the spinal section. However, as the above quotation of Sherrington notes, after a lapse of time the antigravity posture pattern reappears, even in decapitated animals.

*Since the pattern definitely exists when all portions of the brain stem above the pons are removed, the neurones producing it and released by the removal of higher centres must lie in the intact portions of the nervous system, that is, in the spinal cord and small portions of the medulla.* A further proof of this is that section of the cord at the thoracic level allows the same antigravity pattern to remain in the segments below.

Tonic influences which activate muscles in this particular pattern appear to lie both in the medulla and in the afferent fibres of spinal nerves. If either or both of these influences are removed, there ensues a period during which the pattern disappears and flaccidity results. However, the following quotation from Graham Brown<sup>16</sup> indicates that proper stimulation from above may still activate the pattern: "The reactions (of decerebrate attitude) may occur many months after division of the dorsal spinal roots of the arm. That is to say, appropriate stimulation in the region of the mid-brain may evoke an extensor postural tonus or a flexor postural tonus. Sherrington has found that the decerebrate rigidity which occurs after removal of the cerebrum does not occur in a 'de-afferented' limb, but the fact that a condition which at any rate very closely resembles this state may be evoked in such limbs seems to point to the conclusion that the absence of this postural tonus in the decerebrate 'de-afferented' animal is due to the failure of the ascending impulses from the limb which normally play—however, indirectly—upon these mechanisms of the mid-brain, and that the mechanisms themselves, if properly activated, are still able to induce the tonus".

*Pattern and tone constitute two different entities in the nervous system. Tone is the common factor of hypertonic states, and activates*

*muscles in various patterns.* The experiments of Graham Brown (decapitation and de-afferenting) indicate this. When tone is removed, the pattern, like a picture on the wall of a dark room, is not seen but is none the less there in spite of the fact that it is not activated. In brief, tone flows into moulds of patterns much as an electric current. Just as a galvanic current activates flaccid muscles, so does tone, but in addition, it activates them in pattern.

From a consideration of the muscles involved in the flexion and extension phases of gait, as shown by Sherrington, and from all the work on reciprocal innervation, it would be assumed that the neurones for the flexion reflex integration and the reflex standing integration, being corresponding opposites, would be located in the same portions of the nervous system.

From the point of view taken in this article, based upon a neuromuscular conception of movements, the same conclusion can be drawn. From an evolutionary point of view a similar hypothesis must be formulated. When, in the course of evolution, an animal with singly-hinged, fin-like appendages developed appendages with three joints showing the corresponding opposites, the reflexes of flexion and of antigravity posture, it would be natural to assume that the neurones regulating these two newly-appearing reflex activities would lie in the same portions of the nervous system.

## VII.—THE KINETIC AND STATIC TYPES.

The spinal neurones must be activated, or no pattern would be present at all.

In the kinetic types described, the choreiform movements produced the patterns with great consistency. The muscles of the opposite group contracted occasionally (*Cases 2 and 3*). In some cases the kinetic impulse, flowing into lower centres, may produce an apparently patternless picture, as is frequently seen in chorea. These movements, due to their speed, are patternless on ordinary observation, but can, by means of analysis by successive moving pictures, be resolved into definite patterns. In our cases an integration having a clearly definite pattern was exposed to the kinetic impulse. When the opposite of this pattern was activated, it indicated that corresponding opposites were both exposed to the kinetic impulse. Indeed, in reflex stepping we see such a combination beautifully illustrated. Since these opposites constitute a pair of neurone arrangements of the same phylogenetic age, it is natural to find them closely associated.

In the purely spastic variety, *Case 4*, it was found that the tone overflowed not only into those muscles which determined the pattern (triceps), but also into the opposing muscles (biceps). Nevertheless the pattern remained. It would appear, therefore, that though



this tone was distributed to antagonists, *it was distributed subject to pattern. This serves to emphasize the fact that tone flows into pattern and constitutes a separate entity in the nervous system.*

### VIII.—SUMMARY AND CONCLUSIONS.

Abnormal movements and positions are customarily described as such without naming in addition the muscles which produce them. There the matter is allowed to rest for all practical purposes—"the arm and hand are flexed"—"the arms are adducted, the elbows extended, the wrist and fingers flexed". True, certain formulæ for movements exist, such as the flexion of the arm and the extension of the leg of hemiplegic contracture, but the *anatomical relations* of the muscles and nerves causing such groups of movements have never been seriously considered in clinical neurology. Therein lies an error of omission. To draw conclusions about the nervous system from descriptions of movements and positions *alone* is an error of commission.

In this paper it has been shown that there is a well-defined grouping of nerves and muscles under integrating control of the spinal cord, and that it is on the basis of this grouping that formulæ expressing disease in certain parts of the central nervous system of man must be built.

The question of classification of spinal integrations is too lengthy to append here. Suffice it to say that the dorsoventral integrations of the axis (opisthotonic, emprosthotonic) and appendages (rod-like movement of the leg in walking), and the alternating VDV-DVD integrations of the appendages, are those concerned in stepping.<sup>8</sup> In these formulæ the three initials describe respectively the type of movements at the hip and shoulder, knee and elbow, wrist and ankle and below. The alternating formula VDVD-DVDV, which includes both the axis and appendages, is made manifest by decerebration, as we have shown (Section III, C, and Case Reports).

To say, in describing the antigravity posture of decerebration, that the leg is *extended* at the hip, knee, and ankle, the foot *adducted*, and the toes *flexed*, gives no notion of plan or order. To say that there is *adduction* at the shoulder (though *extension* at the hip), *extension* at the elbow and knee, *flexion* and *pronation* at the wrist (though *extension* at the ankle), gives no notion of plan or order. When the facts relating to the grouping of nerves and muscles, not of movement alone, are inserted into the analysis, it is found that the leg and arm formulæ are the same—VDV—and there appears a simpler plan.

Similarly, when the corresponding opposites are considered, the so-called 'flexion reflex' of the arms and legs, there results the same confusion from a consideration of movements alone. The lower

limb is *flexed* at the three great joints, the toes are *extended*, the arm is *abducted* (though the hip is *flexed*), the elbow and knee *flexed*, the wrist *extended* (though the ankle is *flexed*). Here again clearness results from using what is really old information, the basis of which may be found in such text-books of anatomy as Quain<sup>5</sup> and Cunningham<sup>3</sup>. The formula for both arm and leg is DVD, and is opposite to that of the antigravity posture.

The integrations of the spinal cord have clearly defined patterns. By virtue of their activity certain muscles always act together and in the same general way. Their activity may be recognized not only by inspection and palpation, but by changes in position.

The activating forces of these patterns are two—one kinetic and the other static. The latter is familiarly spoken of as tone. Either of these forces activates muscles in clearly defined patterns, provided that a group of integrating neurones is completely released. When a particular integration is patchily involved, such pictures as those of *Case 4* result. In any event, neurones causing pattern and neurones causing tone are not the same.

From the points of view of the physiologist and the pathologist, it is of some importance to recognize that the pattern for the trunk and appendages in decerebration is resident within spinal neurones. It represents the highest spinal integration. The fact that it may appear when lesions are produced as high as the anterior colliculi makes it seem probable that, between that level and the upper level of the spinal cord, neurones producing posture patterns for the trunk and appendages different from those of the spinal cord do not exist. These high lesions simply release the spinal patterns.

Integrations—as, for example, those of the proprioceptive system (labyrinth, cerebellum)—do exist above the upper level of the spinal cord.

Building upon the anatomical grouping of nerves and their end-organs, the muscles, we have gradually come to see an increasing complexity of neurone patterns or arrangements, a manifestation of evolution, of which the dorsoventral integration of progression by hip and shoulder movements (tetrapodal animals) forms one stage, and the folding and unfolding DVD and VDV integrations made manifest in the last two phases of stepping and in decerebration form another and later stage.

With a clearly-defined notion of these and the other simpler spinal integrations established, the study of supraspinal integrations of movement and posture and their significance becomes possible.

We wish to express our thanks to Dr. S. P. Goodhart, Chief of the Neurological Service, for permission to make use of the records of the department.

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# SPIROCHETAL PULMONARY GANGRENE

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## SPIROCHETAL PULMONARY GANGRENE \*

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NEW YORK

Ever since Obermeier, in 1873, reported the presence of micro-organisms of the genus *spirocheta*, or *spirilla*, in the blood of patients with relapsing fever, many diseases have been found to be caused by varieties of this species. The most important disease due to spirochetal infection is, of course, syphilis, to which etiologic relationship of the *Spirochaeta pallida* was demonstrated by Schaudinn and Hoffman in 1905. Castellani subsequently found that frambesia tropica, or yaws, was caused by the *Spirochaeta pertenuis*. The etiologic relationship of spirochetes to Vincent's angina, Weil's disease, rat bite fever and pyorrhea alveolaris has likewise been demonstrated.

It is, however, not so well known that certain pathologic processes in the bronchi and lungs are due to the activity of these micro-organisms. Many years ago, Eichhorst stated that he found spirochetes in the sputum of some patients suffering from bronchitis. Bertarelli and Volpino observed *Spirochaeta buccalis* and *Spirochaeta pallida* in the sputum of patients affected with heart disease. These observations were not confirmed until Aldo Castellani<sup>1</sup> reported two cases of hemorrhagic bronchitis presenting symptoms simulating those of pulmonary tuberculosis, but no tubercle bacilli could be discovered in the sputum either microscopically or by animal inoculation. In these cases large numbers of spirochetes were found in the sputum. Although Castellani pointed out that similar organisms were also found in the saliva and the superficial scrapings of the gums of his patients, he was inclined to ascribe an etiologic relationship of the spirochetes to the pulmonary disease.

From a study of his cases Castellani arrived at the conclusion that, at least in Ceylon, there is a form of bronchial and pulmonary disease caused by spirochetes. To this disease he gave the name of bronchial spirochetosis.

These findings attracted attention and soon many other observers reported similar cases seen in the tropical world. Jackson, Phalen and Kilbourne<sup>2</sup> and Weston R. Chamberlain<sup>3</sup> reported cases from the

\* From the Montefiore Home and Hospital.

1. Castellani, A.: Note on a Peculiar Form of Hemoptysis with Presence of Numerous Spirochetes in the Expectoration, *Lancet* 1:1384, 1906.

2. Phalen and Kilbourne: Report of the U. S. Army Board for the Study of Tropical Diseases made to the Surgeon-General, U. S. Army, Washington, D. C., June 30, 1909.

3. Chamberlain: The Occurrence in the Philippines of Associated Spirochetes and Fusiform Bacilli in Ulcers of the Throat (Vincent's Angina), of the Mouth and of the Skin, and in Lesions of the Lungs (Bronchial Spirochetosis), *Philippine J. Sc.* 6:489, 1911.

Philippine Islands. J. A. Taylor<sup>4</sup> observed several cases of "pneumonia" among the natives of Uganda in which the causative organisms appeared to be spirochetes. He also mentions one case occurring in a European living in Uganda. J. W. Scott Macfie<sup>5</sup> reported cases observed at Accra, Gold Coast Colony, West Africa, and Frank S. Harper<sup>6</sup> noted the condition of a cook living in Tomall, Northern Territories, Gold Coast, West Africa.

That the disease is not confined to tropical countries was made apparent when Ignatz Feldmann<sup>7</sup> and K. Buday<sup>8</sup> reported several cases observed in Hungary. Buday reported many cases of pulmonary gangrene in which a careful macroscopic and microscopic study was made. The spirochetes and fusiform bacilli were found in large numbers in the gangrenous pulmonary lesions.

During the World War many causes of bronchial and pulmonary spirochetes were observed among the tropical troops brought to Western Europe. Likewise, in Europeans who had never been in the tropics, spirochetes were found in the sputum in certain cases of bronchitis and pneumonia, and of patients showing symptoms not unlike those of pulmonary tuberculosis. Thus, cases of spirochetosis bronchialis, hemorrhagic spirochetosis, etc., have been reported by G. Delamare,<sup>9</sup> Dalimier,<sup>10</sup> J. A. Thomson,<sup>11</sup> S. Fischera,<sup>12</sup> H. Violle,<sup>13</sup> F. Barbary,<sup>14</sup> P. Nolf,<sup>15</sup> P. Spehl,<sup>16</sup> and many others in France, Italy, England, Belgium, etc. G. A. Lurie,<sup>17</sup> of Chicago, reported a case observed in a Greek lady residing in Uskub, Serbia. One of us observed in the A. E. F. Hospital Center, Bazoilles, Vosges, France, two cases in Americans (white) not unlike those reported by the authors mentioned. Smears from the gangrenous pulmonary areas made at necropsy showed innumerable mouth organisms, including spirochetes. One of

4. Taylor: Bronchial Spirochetosis in Uganda, with Pneumonic Symptoms, *Ann. Trop. M. & Hyg.* **8**:13, 1914.

5. Macfie: Bronchial Spirochetosis, *J. Trop. M. & Hyg.* **18**:63, 1915.

6. Harper: Bronchial Spirochetosis, *J. Trop. M. & Hyg.* **17**:194, 1914.

7. Feldmann: Beitrag zu den durch *Bacillus fusiformis* und *Spirillum dentium* herangerufenen Infektionen mit besonderer Berücksichtigung der Eiterungen, *Wiener. klin. Wchnschr.* **19**:695, 1906.

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these patients had marked dental caries, and smears from the material in the cavities likewise showed many mouth organisms including spirochetes.

It is noteworthy that even before these reports were made, J. H. Rothwell<sup>18</sup> reported two cases of "bronchial Vincent's angina" with symptoms and signs simulating pneumonia, but in which the sputum was found to be full of spirillae and fusiform bacilli.

More recently Ralph R. Mellon<sup>19</sup> reported a series of cases of whooping cough, pneumonia and empyema from Rochester, N. Y., in

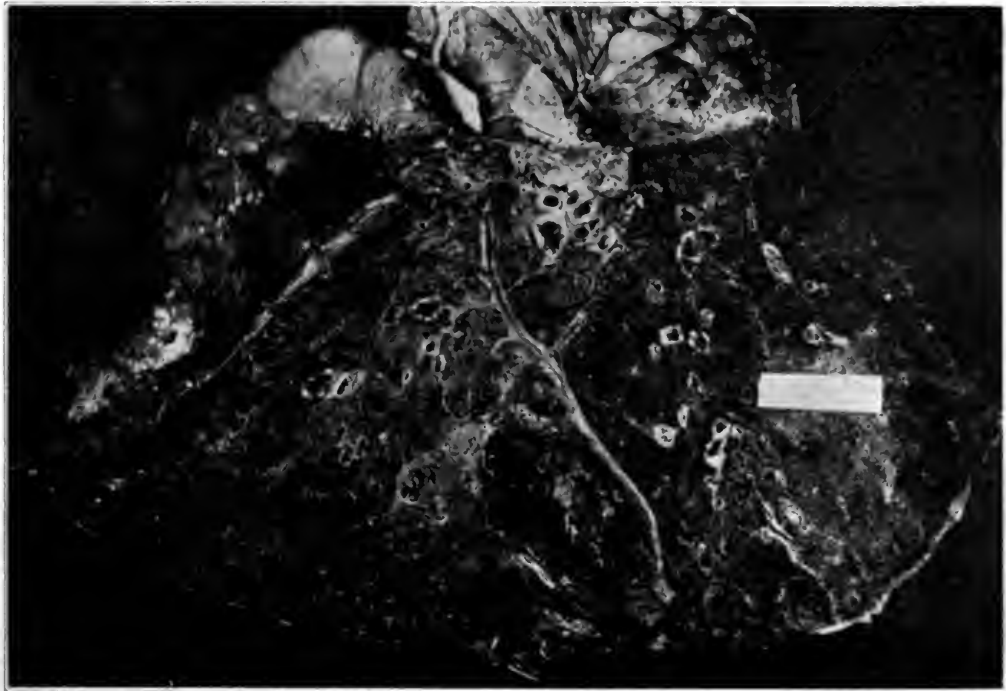


Fig. 1.—Right lung: Extensive bronchopneumonia with gangrenous ulceration in right lower lobe.

which fusiform bacilli were discovered in the sputum. A. N. Sinclair<sup>20</sup> also found in the Philippine Islands numerous cases of pulmonary hemorrhage of tuberculous origin, in which Vincent's spirochetes, or fusiform bacilli were discovered in the sputum. It is his opinion that the presence of fusiform bacilli predisposes to hemoptysis

18. Rothwell: Bronchial Vincent's Angina, *J. A. M. A.* **54**:1867 (June 4) 1910.

19. Mellon: A Clinical and Bacteriological Study of Fusiform Bacillus Infection, *New York State J. M.* **20**:187, 1920.

20. Sinclair: Vincent's Spirochetes and Hemorrhage in Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **4**:201, 1920.

in tuberculous individuals, and that hemorrhage only rarely occurs in incipient cases unless they are present.

The following case of pneumonia with gangrenous ulceration, apparently caused by spirochetes, observed at the Montefiore Hospital, is believed to be the first reported in New York:

#### REPORT OF CASE

M. S. (No. 027757), aged 33, native of Russia, six years in the United States; tailor; admitted April 19, 1920, as a case of pulmonary tuberculosis.

Symptoms on admission: Fever, reaching 105 F., of a continuous type; severe, incessant cough, copious expectoration of foul smelling, greenish mate-



Fig. 2.—Pneumonia with associated gangrenous ulceration. Low power.

rial, at times bloody; dyspnea, cyanosis, prostration. The mental state of the patient precluded obtaining a clear cut and reliable history of the case, but combining the data elicited from him with those given by his friends who visited him at the hospital, we find that his family and personal past history present no conditions which may have had any bearing on his present state. He had been married for eight years, had two children, both alive and well, and had worked at his trade, tailoring, without interruption due to illness, till March 15, 1919, when he began to cough and expectorate. This cough, however, was at the beginning so slight, that he believed it to be due to excessive smoking and he paid little attention to it.

During the first week of April, he was suddenly seized with vomiting, followed by fever and prostration. A physician who examined him at that time informed him that "weak lungs" were responsible for his trouble and advised a trip to the mountains. The severity of the disease prevented his leaving the city. The frequent chills, high fever and sweats became very marked and

he was referred to the Montefiore Hospital with a diagnosis of acute progressive pulmonary tuberculosis.

On admission it was felt that we were dealing with a case of gangrene of the lungs. The foul, sharp, penetrating odor of the breath and expectoration pointed in this direction; the high fever, the sweats and the prostration gave support to this provisional diagnosis. Physical exploration of the chest revealed a suspended area of flatness in the middle of the right side of the chest; this flatness was most marked over the lower two-thirds of the inter-scapular space. On auscultation the breath sounds were found feeble, hardly audible over the flat area, while over the upper lobe of the right lung, medium sized, moist râles were heard; over the right base, in the axillary space, a soft friction sound was made out. There were also signs of fluid in the left pleural cavity, flatness, feeble breath sounds, abolition of vocal fremitus, dullness



Fig. 3.—Smear from gums (Fontana stain), high power. Spirochetes and other organisms.

in Traube's space, etc. These signs elicited on physical examination of the chest suggested either an interlobar empyema which had broken through a bronchus, a pulmonary abscess which may thus have originated, or gangrene of the right lung. A roentgenogram confirmed the findings of physical exploration. A large, somewhat round, shadow, occupying the middle third of the right lung, was disclosed. The rest of the lung showed evidences of hyperaeration.

Of the laboratory findings, the following are of interest: Blood—hemoglobin, 70 per cent.; leukocytes, 21,000; lymphocytes, 18 per cent.; polymorphonuclears, 80 per cent. Wassermann reaction (blood) negative; urea N = 13.7 per 100 c.c.; creatinin, 4.3 per 100 c.c. Urine: acid; sp. gr. 1.022; slight amount of indican; no albumin; no sugar;

Ehrlich's diazo reaction negative; no casts; no tubercle bacilli. Repeated search also failed to disclose tubercle bacilli in the sputum.

Correlating the history with the physical and roentgenographic signs it appeared that the process was not an interlobar empyema. There was no history of an acute onset with pain in the chest, fever, etc., nor has the temperature declined sufficiently to indicate that empyema broke through a bronchus and was being drained. The fetid odor of the expectoration also spoke against an interlobar abscess; there was no history of an acute pulmonary disease such as pneumonia, preceding it. As soon as the patient began to expectorate, the sputum

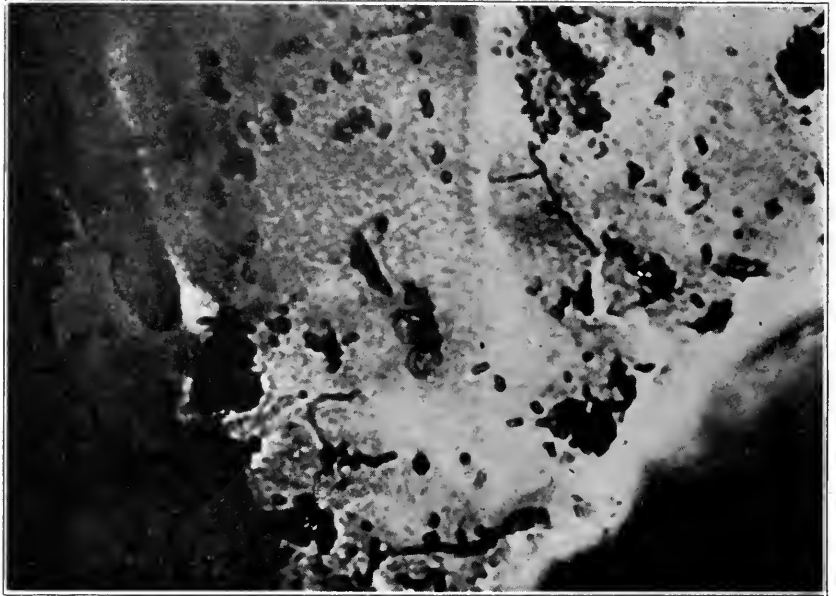


Fig. 4.—Gangrenous lung (Fontana stain), high power. Spirochetes and other organisms.

had the sharp penetrating odor characteristic of gangrene. A foreign body in a bronchus was thought of, but the history, symptomatology and the roentgenogram spoke against it.

The history, symptomatology, physical and roentgenographic signs, combined with the laboratory findings, were thus all against a diagnosis of tuberculosis. As has already been stated, an interlobar empyema was also excluded. The slow onset, the absence of a history of acute pulmonary disease, or operation on the tonsils, etc., also spoke against pulmonary abscess. Furthermore, the expectorated material had the intensely penetrating odor characteristic of gangrene of the lung.

The sputum was then again sent to the laboratory with a request that a careful search be made for spirochetes. With the Fontana

stain, the presence of fusiform bacilli and spirochetes was readily demonstrated. Inasmuch as these organisms are very often found on the gums of healthy individuals, and especially the gums of those who suffer from pyorrhea alveolaris, the sputum was carefully washed, and it was found to contain numerous spirochetes. The material scraped from the gums was then examined and many spirochetes, of the morphology of *Spirocheta microdentium* and *S. macrodentium* were found; some had the morphology of the *Spirochaeta bronchialis* of Castellani. A few had an appearance not unlike that of *Spirochaeta pallida*.

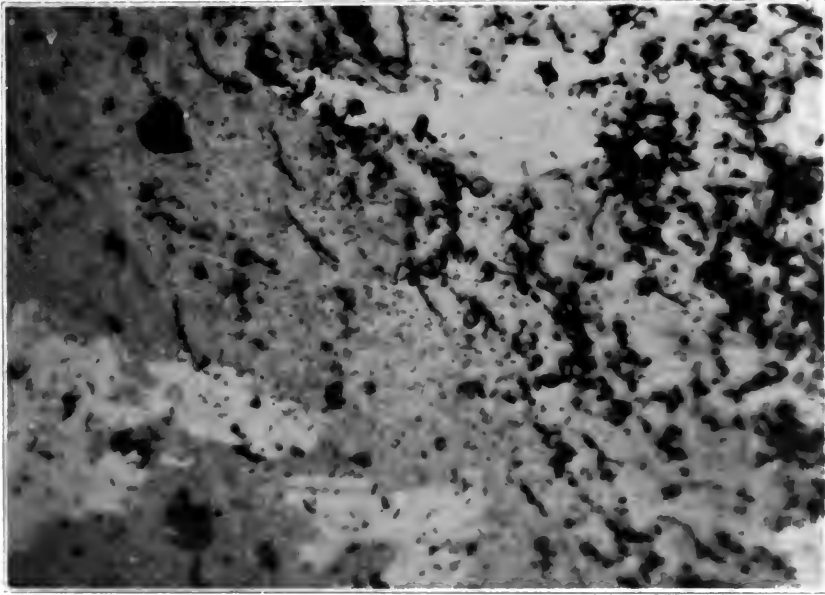


Fig. 5.—Smear from gangrenous lung (Fontana stain), high power. Spirochetes and other organisms.

The usual symptomatic treatment apparently had no effect on the progress of the disease. The fever remained high, between 103 and 104 F.; cerebral symptoms made their appearance and the prostration remained severe. The foul odor of the expectoration and the weakness of the patient increased. Reports have shown that in some cases of abscess and gangrene of the lung, artificial pneumothorax has proven of value, though in the experience of one of us, it has never been a success in this class of cases. On entering the right pleural cavity with the pneumothorax needle May 5 we found excellent negative pressure with respiratory oscillations and allowed 400 c.c. of air to enter. The intrapleural pressure remained minus 10 after the initial inflation.

No improvement was noted in the general condition of the patient after the pneumothorax was induced. The fever remained high, the prostration continued, and the weakness increased. May 6, the cerebral symptoms became accentuated, the patient died at 4:30, manifesting intense dyspnea and cyanosis.

For special reasons a complete necropsy could not be made; only the thoracic and abdominal viscera were removed for examination.

The lungs showed extensive coalescing lobular and bronchopneumonia of both upper lobes and the right middle lobe. In the right lower lobe, associated with the consolidated lung, there was extensive gangrenous ulceration, the ulcerated areas varying in size from several millimeters to a cavity 4 cm. in diameter.

Microscopically, the picture was that of extensive lobular and bronchopneumonic exudation with numerous areas of necrosis and gangrene. With Fontana and MacCallum stains, spirochetes and fusiform bacilli were observed in large numbers in the necrotic and gangrenous areas. The following is an abstract of the necropsy protocol:

#### NECROPSY PROTOCOL

The larynx and upper part of the trachea were not removed. The lower portion of the trachea and right bronchus show an intensely injected, swollen mucosa. In the lumen, there is a considerable amount of mucopurulent material. In the left pleural sac, several hundred c.c. of thin, blood tinged fluid were found.

**Lungs:** All lobes much more voluminous than usual. The upper lobes cushiony, soggy; middle and lower lobes soggy, solid. The pleura is thickened over the upper lobes and over the posterior portions of the lower lobes. There are sheetlike, fibrous tags in these areas. There is some fibrinous exudate over the lateral and median portions of both lower lobes. Glands at the hilum enlarged, pulpy, edematous, injected, pigmented. On section of the upper lobes, a moist, dark red surface presents. The tissue is apparently congested and edematous. There is no definite consolidation. There is a considerable amount of thin fluid in the air sacs. The bronchial branches show an injected, swollen mucosa, overlaid by blood tinged, mucopurulent material. Right middle lobe on section, shows extensive consolidation, the patches small, several millimeters to one centimeter in diameter, almost adjoining one another throughout the lobe. These areas are soft, yellowish, almost purulent. They are, however, considerably more coherent than abscesses. Both lower lobes on section show extensive, patchy consolidation, the patches almost adjoining each other throughout the lobes. This is especially true in the posterior portions. The patches in these lobes also vary in size from several millimeters to one centimeter. They vary in color from reddish yellow to dark green. The latter color is especially marked in the right lower lobe. In addition, many of the dark green, consolidated patches show central ulceration. The cavities vary in size from a few millimeters to four centimeters in diameter. The large cavity is present in the upper anterior portion of the right lower lobe, well below and median to the apical portion. There is no sharp reaction zone about the cavities. They are all surrounded by greenish, consolidated lung. Within the cavities, there is thin, greenish, necrotic material. The ulceration in the left lower lobe is much less advanced than in the right lower. The bronchial tree throughout, shows beginning calcification of the cartilages. The mucosa is swollen, injected, overlaid by mucopurulent material. In places, espe-

cially in the right lower lobe, the mucosa has a greenish tint. The lungs have an intense, penetrating, disagreeable odor.

Smears from the yellow and green consolidated areas and cavities show innumerable, gram-negative spirillae and spirochetes resembling *Spirochaeta microdentium*, *S. macrodentium* and *S. refringens*, the latter present in small numbers. Throughout the smears there are also innumerable gram-negative bacilli. Some of these are small, resembling *Bacillus influenzae*; others are larger. Some of the larger gram-negative bacilli have a safety-pin appearance, resembling colon bacilli. In addition, there are a large number of rounded, gram-negative cocci and some diplococci. In the smears the following gram-positive organisms were noted: innumerable diphtheroids, many rounded cocci, rounded and lancet shaped diplococci, scattered small chains of rounded cocci, also scattered, straight and curved, beaded bacilli with tapering ends about the size of gas bacilli and somewhat smaller.

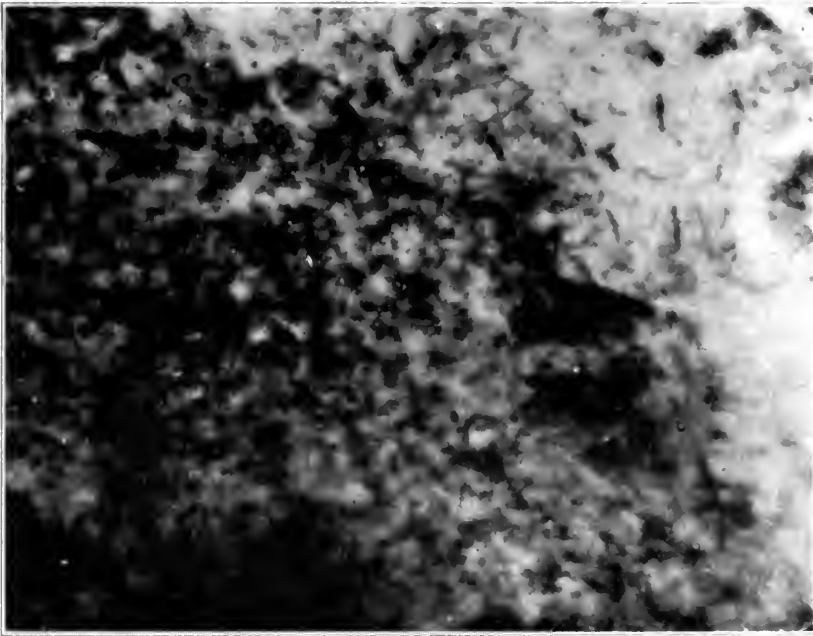


Fig. 6.—Section of gangrenous lung (MacCallum stain), high power. Fusiform bacilli and other organisms.

**Microscopic Sections:** Section 1 shows on gross inspection a number of circumscribed areas from one to several millimeters in diameter with pink periphery and bluish center. Alveoli in general apparently filled. Under low power, the circumscribed areas mentioned above are seen to be composed of a zone of necrotic pink stained lung tissue and exudate, the central portions bluish, consisting of masses of organisms. There are many of these necrotic areas in the section; in places they adjoin one another; in places they are discrete and vary in size from that of a glomerulus to several millimeters in diameter. In addition to these areas, the alveoli throughout the section in general are filled with exudate composed of swollen alveolar cells and amorphous pink stained material and a few wandering cells. The alveolar walls, in general, show swollen epithelial cells with blood vessels moderately engorged. In places, the alveoli are filled in great part by red blood cells. Portions of the pleura in the section are swollen, distended by amorphous

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pink stained material, red blood cells and scattered wandering cells. There is a small amount of fibrin present. In places there is definite beginning organization of the exudate.

Section 4 shows in addition to circumscribed necrotic areas with masses of blue stained organisms, the adjoining alveoli filled with pus cells and mononuclear cells, the nuclei of the majority of these being deeply stained (pyknotic). External to the alveoli filled with pus cells, are alveoli filled with large mononuclear cells, some containing blood pigment, some pus cells, some red blood cells and some amorphous pink stained material. The pulmonary vessels throughout are engorged. In this section there are numerous groups of alveoli filled with exudate rich in polymorphonuclears; in places there is definite necrosis of the exudate. In places there are circumscribed masses of blue stained organisms. There are scattered bronchial branches filled with necrotic exudate containing blue stained organisms, the epithelium of these bronchial branches is almost homogenously pink stained, the nuclei being barely visible. Throughout all coats of bronchial branches the blood vessels are engorged. There is apparently considerable thickening due to the presence of granulation tissue. In places, in the section the alveoli contain in great part amorphous pink stained material (serum) and scattered, desquamated cells. In places, the exudate is present in the peribronchial alveoli, in places the exudate is apparently lobular in distribution and varies in proportion of serum, large phagocytic mononuclear cells, pus cells and red blood cells. In places, there is definite organization of the exudate; in other places there is necrosis and ulceration associated with blue stained masses of organisms.

Section 5 shows a wall of a large cavity composed of amorphous pink stained necrotic material in the innermost zone, external to which there is granulation tissue composed of numerous engorged capillaries and fairly densely layered connective tissue cells. In places, the connective tissue cells are loosely connected. In places, there are numerous plasma cells in the granulation tissue. External to this zone there are numerous, somewhat collapsed alveoli filled with exudate, varying in character, as described above. In this section also there are fair sized bronchial branches with greatly thickened walls, due to granulation tissue.

Sections of the lung stained by Fontana method show in the necrotic areas a considerable number of spirochetes resembling *Spirochaeta macrodentium* and *S. microdentium*. With this stain, innumerable other organisms are observed in the necrotic and consolidated portions. Sections stained by MacCallum's stain show in the consolidated and necrotic areas innumerable gram-positive organisms including gram-positive bacilli, some of these having the morphology of diphtheroids; gram-negative bacilli, some having the morphology of influenza bacilli, also gram-positive and gram-negative cocci. There are also many large slightly curved gram-positive bacilli, not unlike the fusiform bacilli of Vincent's angina. The spirochetes are poorly stained by this method. With this stain the predominant organism is the somewhat gram-positive bacillus.

#### DISCUSSION

The presence of numerous spirochetes in the gangrenous portions of the lung in the case reported, suggests their etiologic relationship to the lesion. It is probable that the spirochetes responsible for the gangrene in this case are of the type Castellani calls *Spirochaeta bronchialis*. While, of course, there are present in the lesions numerous mouth organisms, the overwhelming number of the spirochetes, as well as the study of their location in the diseased area, and the cellular reaction to their presence, compels the conclusion that the predominantly gangrenous lesions are to be directly attributed to the spirochetes.



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## THE DIAGNOSIS OF INTRATHORACIC NEOPLASMS.\*

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DURING the past five years thirty-three cases of primary malignant neoplasms of the bronchi, lungs, and pleura have been admitted to the Montefiore Hospital. This appears to be a larger number than any other hospital has reported within such a comparatively short period, and we were at first inclined to attribute it to our diligence in looking for this class of cases. The fact that of the thirty-three cases admitted, only four were diagnosed correctly before admission to the Montefiore Hospital appeared to speak in favor of such a view. But further inquiry points altogether in another direction.

There appears to have occurred an increase in the absolute, as well as the relative, number of cases of primary malignant neoplasms of the lungs. This increase has, however, been noted mainly by

\*Read before the Section of Medicine, New York Academy of Medicine, February 15, 1921. (For discussion, see page 540.)

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pathologists while making autopsies; most cases had been otherwise diagnosed during life. Statistics published from the various pathological laboratories in Europe are to this effect, and in this city, Dr. Douglas Symmers informs us that in the twelve years previous to July 19, 1919, he encountered five examples of primary malignant neoplasm of the lungs in the Pathological Laboratory of Bellevue Hospital, and from July 19, 1919, to December 20, 1920, he saw eight cases.

Of the thirty-three cases that have been observed at the Montefiore Hospital during the past five years, complete autopsies have been obtained in sixteen, and in three surgical autopsies. It is worthy of mention that in all but one the diagnosis was made during the life of the patients, while in only one case was the diagnosis of the disease found at the autopsy to be an error. It is our conviction that the cases on which this communication is based were diagnosed during life of the patients because we relied mainly on purely clinical methods, on the history, symptomatology, course, and physical signs, while other diagnostic and laboratory methods, such as cytology of excretions and exudates, and radiography, were invariably considered as of merely confirmatory importance.

Nearly all our patients, before admission to the Montefiore were in other hospitals or clinics, where efforts at making a diagnosis had been made. The result was that the thirty-three patients were referred to us with the following diagnoses: Cancer of the lung, 4; pulmonary tuberculosis, 13; pleurisy with effusion or empyema, 7; chronic pneumonia, 2; cardiac disease, 2; neurosthenia, 1; abscess of the lung, 2. Despite this variety of diagnoses on admission, in two-thirds of the number of cases

we either diagnosed tumor of the lung at the first examination of the patients, or at least suspected it. The purpose of this communication is mainly to show how we are led to make this diagnosis; the details of these cases will be given in a later communication.

It seems that malignant growths of the lung are so often missed because it is considered an exceedingly rare disease, and is never thought of when an atypical case of some more common pulmonary disease is examined. The fact that the onset is insidious, with cough, expectoration, pain in the chest, dyspnea fever, hemoptysis, and that the physical signs are usually those of a localized airless area of lung tissue, is responsible for the large number that are mistaken for pulmonary tuberculosis. In 50 per cent. of cases pleural effusions, serous, sanguineous, or purulent, occur; and for this reason, a large proportion are treated as pleurisy. In the later stages, when the tumor disintegrates, cavities are formed in the lungs, and fetid sputum is expectorated, thus abscess or gangrene of the lung is simulated. However, a careful scrutiny has shown that nearly all cases have certain characteristic traits which betray the presence of a new growth in the chest, provided it is always borne in mind that this disease is a possibility in all aberrant chronic pulmonary conditions in persons of the cancer age.

Nearly all patients with malignant growths in the chest cough and expectorate sputum which is not unlike that brought out by tuberculosis patients. Of course, no tubercle bacilli are found on repeated examinations. But in about one-half the number, hemoptysis was an early symptom. At first the blood is scanty, though the streaky sputum of

phthisis is rare. Usually the sputum is thoroughly mixed with blood, and it thus presents the appearance of raspberry juice or current jelly. In the later stages, when disintegration of the tumor takes place, there may be copious and uncontrollable pulmonary hemorrhages; one of our patients succumbed to such a hemorrhage.

But there are two early symptoms which are hardly ever seen in early phthisis, namely, dyspnea, and pain in the chest. *It is important to think of a pulmonary neoplasm when a patient in the cancer age, showing no symptoms of cardiac, renal, or arterial disease, begins to cough, and is short winded.* In the advanced stages of tuberculosis severe dyspnea is at times encountered, but then the history and physical signs show extensive destruction of lung tissue, a pleural effusion, or a pneumothorax. The dyspnea in cancer is due to the plugging of a large bronchus from within or from without; when a primary bronchus is thus obstructed by the growth, or the trachea is pressed upon, the dyspnea may be severe, agonizing. Sudden death from asphyxia has thus occurred in two of our cases. Other pressure phenomena seen in lung tumors include pressure against the large veins, especially the superior vena cava, when the tumor extends into the glands of the mediastinum along the lymphatics. The result may be edema of the upper part of the chest, neck, and face. In some cases the tumor extends into the right ventricle, or is pressing against it, producing intense dyspnea, cyanosis, edema of the entire body, etc. Pressure against the esophagus may result in difficulties in deglutition; in two of our cases it led to inanition. We have had cases in which the dyspnea was paroxysmal, owing to pressure which

was more or less relieved on moving the body in certain directions. Stridor is very rare; we encountered it only in three of the thirty-three cases.

Pain, next to dyspnea, is a constant symptom; it was present more or less in thirty-one out of our thirty-three cases. It is usually felt in the lower part of the chest, in the axillary region, and in the shoulder, radiating to the arm, forearm, even to the finger tips. It is frequently misinterpreted and ascribed to pleurisy or intercostal neuralgia. However, the acute onset, friction sound, etc., of acute pleurisy are absent. In pleurisy with effusion, the pain is ameliorated, or disappears after an effusion takes place, while in tumor it remains after an effusion occurs, or may even become more pronounced. *In patients who have passed middle age, pain in the chest, with or without a pleural effusion, is suggestive, and requires careful investigation.*

In attempts at differentiation from pulmonary tuberculosis we are at times baffled because of fever which occurs in the majority of cancer cases very early, and in many even night-sweats have been noted. The fever may be mild, running up to over 100° Fahr. in the afternoon and normal during the morning. It may be high in the later stages, 103° to 104° Fahr., continuous, remittent, or intermittent. This in patients with cough, profuse expectoration, hemoptysis, etc., showing signs of a localized lesion in the chest, exquisitely simulates advanced pulmonary tuberculosis. It is for this reason that so many cases were sent in to us with that diagnosis. But in that vast majority of cases physical exploration of the chest decides the diagnostic problem.

Enlargement of the superficial glands is a late symptom, and when this is found the tumor in the

lung is, as a rule, quite extensive. These glands are usually found on the neck, between the heads of the sternomastoid, and require careful palpation to be elicited as small hard nodules, freely movable. When at a later stage the glands are very large and visible on inspection, the axillary glands are also found enlarged. Only in rare and far advanced cases are the inguinal glands enlarged, indicating extensive metastasis. Enlargement of the superficial veins of the chest and shoulder is seen only in cases in which metastasis has occurred into the mediastinal glands, and this is uncommon.

The diagnosis is made by physical exploration of the chest and, in our experience, it has been more often decisive than any other diagnostic method. In many cases a small tumor nodule is more easily and much earlier discerned by percussion and auscultation than by radiography. We have mainly relied on the flat note elicited by percussion over the site of the tumor, and the flat area is, as a rule, much more extensive than the size of the growth, because it obstructs a bronchus, thus cuts off the air supply of the lung supplied by that tube. This flatness is found in the upper lobe of the lung, or runs across the chest—is suspended—or is elicited over the lower lobe of the lung, according to the location of the tumor and the bronchus it obstructs. In a few cases, when the tumor does not obstruct a bronchus, it may be found by percussion, which shows a flat area extending a few inches away from the border of the sternum anteriorly, or from the spine posteriorly. At times we found flatness anteriorly, while posteriorly the note was normal or even hyperresonant.

Flatness in the lower parts of the chest commonly denotes pleural effusion, or a thick pleura;

in the upper lobe it simulates a tuberculous lesion. But tuberculous lesions of the upper lobe emit a dull note, never a flat one. This is always to be borne in mind.

Auscultation will show feeble, or complete absence of breath sounds when a bronchus is obstructed. It is noteworthy that this may be found in cases with very small growths, provided a large or medium sized bronchus is obstructed, which is true of a very large proportion of cases. In cases in which the growth is in the region of the upper lobe the absence of breath sounds shows that we are probably not dealing with a tuberculous lesion in which the note is never flat, and there are nearly always audible some altered breath sounds, broncho-vesicular, bronchial, or cavernous. In cases with flatness running across the middle of the chest, or involving the lower half of the chest, absence of breath sounds points to pleural effusion, either interlobar or general. The absence of adventitious sounds shows that in upper lobe cases we are not dealing with tuberculosis, while in middle and lower lobe cases it again points to pleural effusion. The same is true of the vocal fremitus, which is feeble, or more commonly absent over the affected area. However, the history of the case is usually sufficient to rule out pleural effusion: the acute onset is lacking and the persistence or aggravation of the pain in the chest, despite the evidences of fluid, points to a tumor.

In many cases the growth does not completely compress a bronchus, but only narrows it, and air is still permitted to pass through the narrowed tube. Here we get bronchial, or even amphoric breath sounds, which has been called by some writers *cornage*. When heard near the border of the ster-

num, or in the interscapular space, especially its upper half, in a patient in whom the note over the upper lobe of the lung is flat on percussion, and no adventitious sounds are audible, it is characteristic of tumor of the lung. It simulates a cavity, but the flatness and the absence of adventitious sounds point to a tumor.

Many lung tumors break down, and the patients expectorate large masses of sputum, have profuse hemorrhages, run high-fever, sweat, etc. In these cases signs not unlike those of tuberculous cavities are elicited on physical examination, and, in fact, most of them are treated for tuberculosis. However, of the 15 cases of this type that have been sent in to the Montefiore Hospital as tuberculous, nearly all were differentiated within a few days after admission. We have relied on the following diagnostic criteria: The history of the cases, the fetid sputum lacking in tubercle bacilli, the freedom of the opposite lung from signs of pathological changes, the flatness of the percussion note, etc., all point in the direction of a tumor. In doubtful cases the induction of an artificial pneumothorax and the taking of a radiogram may clear up the diagnosis, as has been described elsewhere. (See *Journ. Amer. Med. Assn.*, 1921, lxxvi, p. 581.)

With the appearance of pleural effusion, which occurs in over 50 per cent. of cases, things change and the difficulties in diagnosis multiply. Signs of the effusion are easily detected and a favorable prognosis is given. If exploratory puncture reveals pus, an operation is resorted to and the surgeon wonders why, after weeks of careful draining, there seems to be no tendency for the lung to expand and the wound to heal.

Experience with a comparatively large number of



these cases has taught us that effusions secondary to pulmonary neoplasms have certain characteristics which betray the new growth. It seems that in these cases the fluid accumulates very rapidly and completely fills the chest. Inflammatory effusions, on the other hand, fill only part of the chest and rarely reach above the fourth or third rib. For this reason, in inflammatory effusion percussion shows a lower zone of flatness above which the resonance is slightly tympanitic—Skodaic. When there is a tumor behind the effusion, or when the growth originates in the upper lobe of the lung, a flat note is elicited all over the affected side of the chest, from above the clavicle to the lower margin of the thoracic wall. *It is important to think of a lung tumor when one side of the chest is flat and offers the characteristic resistance to the pleximeter finger from the clavicle to the base.* Likewise, absence of breath sounds over one entire side of the chest, excepting cornage mentioned above, if not due to a pneumothorax, which is excluded by percussion, is almost invariably due to a tumor of the lung or pleura with an effusion.

In cases presenting these signs careful investigation will usually reveal other symptoms and signs confirmatory of the pathological process in the lungs—enlarged glands will be found on the neck, the mediastinum will be found displaced, though in shrinking tumors of the pleura it may be drawn toward the affected side; pain in the chest will be complained of, which cannot be accounted for by the more common clinical conditions.

In attempting differentiation from more common diseases of the lungs and pleura, the following points have proven of value: Enlarged glands of the neck may be due to cancer of the lung, tuber-

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• culosis, or Hodgkin's disease. Hodgkin's is differentiated along the usual lines of diagnosis of this disease. But tuberculous glands have one characteristic which, if borne in mind, will spare many errors: *Patients with enlarged tuberculous glands on the neck hardly ever have signs of active disease in the lungs, while when the glands are malignant we find signs of extensive changes in the lungs.* Dense consolidation of lung tissue, revealing itself by flatness, absence of breath sounds, etc., is an indication that the enlarged glands on the neck are malignant, and not tuberculous.

Many cases have been admitted with symptoms and signs of abscess or gangrene of the lung, and the signs elicited by physical examination apparently confirmed these diagnoses. However, abscess and gangrene of the lung are almost invariably preceded by some acute inflammatory disease of the lung, especially pneumonia, or by the aspiration of a foreign body. They have a history of sudden onset with a definite symptomatology. When the fever, cough, and expectoration of fetid sputum are due to a disintegrating cancer of the lung, a history of an insidious onset will be obtained. We have found it expedient to suspect all cases of "abscess of the lung" in persons of the cancer age of malignant disease of the lung, and to delve carefully into the history, symptomatology, and course of the disease, while the physical signs usually clinch the diagnosis.

We have made use of nearly all the laboratory aids in diagnosis, and found them in a few instances confirmatory of the clinical findings, but in most cases they prove either of no value or altogether misleading.

In three cases cancer cells were found in the

sputum. But only when the tumor disintegrates, and parts are expectorated will these cells make their appearance in the sputum, and this is rather late for a diagnosis. Routine clinical methods prove decisive much earlier, as we have shown.

Moreover, cells not unlike those of malignant tumors may be found in the sputum expectorated by patients suffering from any disease of the bronchi, lungs, or throat. The large number and variety of epithelial cells which are derived from the epithelial linings of the mouth, nose, throat, and bronchi, and some, even, from the esophagus, may deceive the most competent pathologist. In fact, in most cases in which we have sent the sputum to the pathologist for intensive study of its cytology, his report has invariably been rather guarded, which did not permit absolute reliance, such as is given in a report of the finding of a specific organism.

Likewise, examination of the pleural exudate has been of but little value. It is very frequently sanguineous. Of 21 effusions, 4 were sanguineous. This is not a very high proportion, and when we consider that it is sanguineous at times in tuberculous effusions, its diagnostic significance wanes. However, in persons over 35 with a history of an insidious onset and pain in the chest, dyspnea, etc., it is suggestive. It may be purulent: in 5 of our cases it was so. Examination of the sediment of the fluid obtained by exploratory puncture has also given us but little help in diagnosis. Hardening the sediment and cutting and staining it have been attempted in several cases. But a comparison of findings with those obtained in tuberculous pleurisy hardly shows any difference. In two cases the cytology was suggestive of cancer cells, but it was never conclusive.

Of greater utility has been found radiography in lung tumors, but in many cases it proves misleading or negative. In the vast majority of cases it could not be considered of final value. A small tumor may altogether escape registration on the plate. In 2 cases of extrathoracic cancer, physical exploration of the chest revealed physical signs strongly suggestive of metastatic deposits in the lungs. The radiographic plate taken at that time showed nothing to lead one to suspect a tumor in the indicated area. But about 4 weeks later, when the tumor had grown, it was discovered on the plate. It is thus clear that a small tumor, provided it impinges on a bronchus, or grows within it, may be discovered by careful physical examination much earlier than the *x*-rays will clearly reveal it.

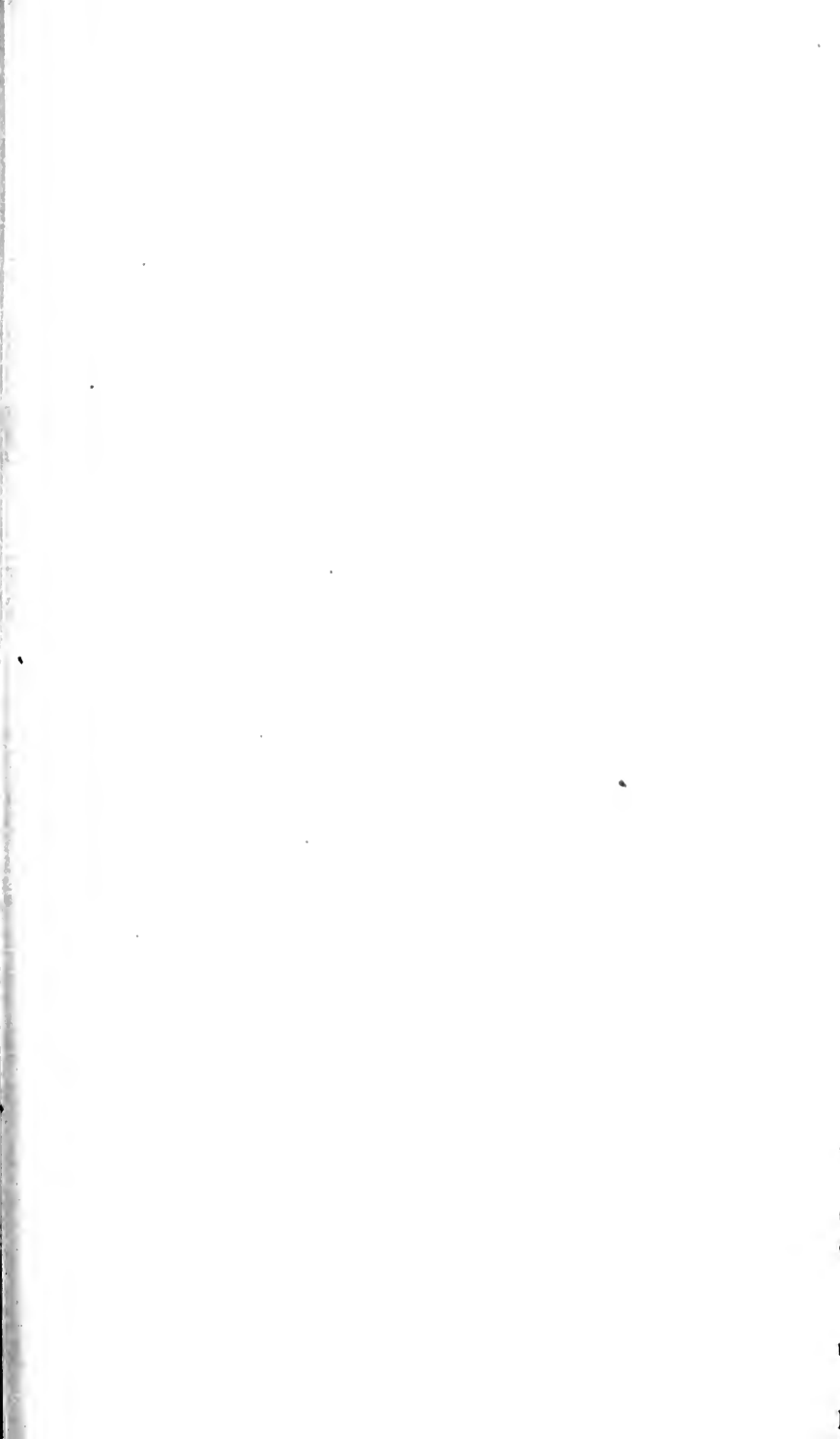
Moderate sized and large tumors appear clearly on the plate as homogeneous shadows, sharply defined. In some cases there is no line of demarkation, and then it may be easily mistaken for other pulmonary lesions. Now and then an interlobar effusion will exquisitely simulate a tumor of the lung. Likewise, miliary carcinomatosis cannot be differentiated from miliary tuberculosis on the plate. When fluid appears, and it does in over 50 per cent. of cases, it covers up the tumor and the radiographer can only report an effusion. This, in fact, is the source of a large proportion of errors in diagnosis. It appears, however, that when the shadow cast by the fluid fills the entire half of the chest, radiographers are justified in suspecting a tumor of the lung or pleura. But, after all, only the history and physical signs have proved decisive in our cases. Nearly all our cases of this sort went to the radiographer with the suggestion that we

consider the possibility, or that we are convinced that there is a lung tumor.

We have resorted to the following procedures: Withdrawing the fluid and immediately taking a radiogram will show a tumor which is otherwise obscured by the fluid. Of late we withdraw the fluid and produce a pneumothorax, then a radiogram will show the tumor clearly and unequivocally.









## INTRATHORACIC EQUILIBRIUM IN PNEUMOTHORAX

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Although artificial pneumothorax has become a well recognized therapeutic procedure, ever gaining wider application in the management of pulmonary tuberculosis, the consideration of the pneumodynamics involved and the altered intrathoracic conditions consequent to its induction have received practically no attention. Indeed, so few are the references to this important subject in the rapidly accumulating literature on pneumothorax, that one questions whether the far-reaching effects of these altered intrathoracic conditions on the untreated side and circulatory apparatus are often properly evaluated.

The mechanism of these various intrathoracic changes is as intricate as it is fascinating; and it will be the purpose of this paper to discuss in some detail the factors determining intrathoracic equilibrium in pneumothorax with especial reference to their practical significance in this form of therapy.

It will not be amiss, for the sake of clearness, to begin the discussion of the main topic by a definition of terms used and a summary of the accepted conception of the genesis of the negative intrapleural pressure.

Intrathoracic pressure, as is well known, is the pressure exerted on the mediastinal organs. It is equal to the atmospheric pressure minus the opposing tension exerted by the expanded lung, that is, the elastic recoil of the lung. The negative intrapleural pressure is equal to the elastic force of the stretched lung. It is greater the more the lung is expanded, and vice versa. This pressure equals in the adult about  $-7$   $-9$  cm. of water on inspiration and  $-3$   $-5$  on expiration.

As to the genesis of negative intrapleural pressure, it is of importance to recall that in the newborn infant the lungs fill completely the thoracic cavity and that there is no measurable negative intrapleural pressure. At each expiration the lungs are completely emptied and there is, therefore, practically no reserve supply of air in them. However, this lack of air reserve is compensated by the more perfect ventilation of the

alveoli. That life is possible under such conditions is perfectly obvious. Yet we have here a condition amounting to partial bilateral lung compression.

In the eight-day old infant the negative intrapleural pressure was found by Hermann (1) to be only 0.4 mm. of mercury. The negative intrapleural pressure observed in the adult thorax is developed gradually. It is due to the fact that the size of the thorax increases more rapidly and to a greater extent than the lungs which the thorax contains. To fill this enlarging cavity, the lungs, which are elastic bodies, become more and more expanded and thus the negative intrapleural pressure is established. In the fully developed respiratory mechanism the reserve supply of air in the lungs is created gradually, and this at the expense of the ventilation of the alveoli, which, during the separate respiratory cycles, is less perfect in the adult than in the newborn infant. The bearing of all this on the subject under discussion will become apparent as we go on.

#### INTRATHORACIC EQUILIBRIUM IN PNEUMOTHORAX

By allowing filtered air to enter the pleural space on one side until the intrapleural pressure is equal to atmospheric pressure, the elastic recoil is compensated for and the lung will assume its so called normal size. A smaller amount of air introduced into the pleural cavity will only partially counteract the elastic recoil of the lung, and its collapse will be proportionately incomplete. On the other hand, when we force air into the pleural cavity under pressure greater than atmospheric, the lung, on account of its elasticity and compressibility, will be caused to assume an even smaller volume than the so called normal.

In all these instances the intrathoracic pressure will be variously increased in the same proportion as the negative pressure is decreased or even changed to positive. Under these circumstances the mediastinal structures will be subjected to increased pressure on the pneumothorax side and will be pushed to the untreated side, unless they are fixed by adhesions, as frequently occurs in tuberculous chests.

When the mediastinum is effectively fixed by adhesions, the effect of the increment in the intrathoracic pressure on the pneumothorax side will not make itself felt on the pressure conditions in the untreated hemithorax. But when the mediastinum is relatively free from adhesions, the increased intrathoracic pressure on the treated side will have the following effects on the intrathoracic pressure and size of the untreated

side, as well as upon the relative position of the various thoracic structures:

1. The relatively flexible mediastinum will be put on a stretch and pushed to the opposite side. The degree of such displacement will depend on the amount of the intrathoracic pressure in the pneumothorax side, the degree of the elasticity of the mediastinum, and the extent of the relative fixation of the mediastinal structures through adhesions or otherwise.

2. The size of the untreated hemithorax will be proportionately decreased and, because of this, its intrapleural pressure will be proportionately less negative.

3. The intrathoracic pressure on the untreated side will be proportionately increased and will be equal to the intrathoracic pressure on the pneumothorax side minus the elastic recoil of the stretched mediastinum.

In other words, intrathoracic equilibrium is established in pneumothorax as under all normal conditions. The change in pressure in one hemithorax must be balanced by appropriate changes on the opposite side; and it is in response to this fundamental principle that certain so called "movements of balance" take place in the chest cavity in pneumothorax.

#### MOVEMENTS OF BALANCE

Perhaps the best illustration of the delicate sensitiveness of intrathoracic equilibrium in pneumothorax and of the manner in which it is maintained, is found in the "pendular movement of the mediastinum" and the "paradoxical movement of the diaphragm." These so called "movements of balance" are well known and are frequently observed, jointly or individually, in the radioscopic studies of pneumothorax.

By "pendular movements of the mediastinum" is meant the inspiratory displacement of the mediastinum towards the pneumothorax side, slight or marked, depending on its relative freedom from adhesions, its elasticity, and the pressure conditions in the thorax. The "paradoxical movement of the diaphragm" consists of the loss of coördination in the contraction of the two halves of this muscle; while the diaphragm is lowered on the untreated side during inspiration, it is simultaneously raised on the side of the pneumothorax, and vice versa.

Barjon (2), after a study of a large number of cases of pneumothorax, summarizes the indispensable condition for their production. He states

that the phenomenon of the "paradoxical movements of the diaphragm" is determined by the following four indispensable conditions: (1) Freedom from adhesions. (2) Absolute inertia of the diaphragm, that is, paralysis of the diaphragm, making it an inert membrane easily affected by differences in pressure. (3) Complete suppression of the respiratory function of the lung, brought about by its complete collapse when free from any adhesions. (4) Maintenance of moderate positive pressure on the pneumothorax side. The intrapleural pressure must be equal to or slightly greater than atmospheric pressure. It must be just enough to prevent air entering the collapsed lung during inspiration, but not high enough to force and keep the diaphragm down.

By substituting in the above statements the word "mediastinum" for the word "diaphragm" he formulates the essential conditions necessary to produce the "pendular movement of the mediastinum."

Barjon's discussion of the subject is quite elaborate and very interesting. It seems to us, however, that the "movements of balance" can be explained on the basis of the fundamental principles governing the labile intrathoracic equilibrium in pneumothorax discussed in the earlier part of the paper. Indeed, the radioscopic study of the "movements of balance" in the pneumothorax cases in our institution has convinced us that the mechanism of their production is relatively simple, and that most of the conditions described by Barjon as essential and indispensable may be lacking although the phenomenon can be clearly demonstrated.

From a larger group showing these movements of balance to a greater or lesser degree, we have selected three representative cases which we think will best illustrate these phenomena and suggest their mechanism.

#### PRESENTATION OF CASES

*Case 1.* (Figures 1 and 2.) Figure 2 represents the position of the thoracic viscera after a deep inspiration and figure 1 represents their position after a forced expiration. The marked inspiratory displacement of the mediastinum is perfectly evident. It is to be noted that there is a definite, large, apical adhesion on the pneumothorax side, and that the right lung is incompletely collapsed and is partially functioning. It may be added from the clinical record that the intrapleural pressure on the pneumothorax side was distinctly negative ( $-5-3$  cm. of water). In other words, of the four conditions described by Barjon as absolutely essential and indispensable for the production of the pendu-

lar movements of the mediastinum, three were absent in this case. It will therefore be instructive to analyze in some detail the exact mechanism of this phenomenon as it was observed in this case.

*Analysis of Phenomenon.* In any phase of the respiratory cycle there is a balance of pressure in both hemithoraces, as well as in the mediastinal



FIGS. 1 AND 2. CASE 1

FIG. 1. Taken in forced expiration. Note short distance of right cardiac border from midsternal line.

FIG. 2. Taken in deep inspiration. Note increased distance of right cardiac border from midsternal line, definitely showing inspiratory displacement of mediastinal structures toward pneumothorax side. "Pendular movement of the mediastinum."

region, that is, intrathoracic equilibrium exists. During deep inspiration there is a momentary disturbance of this equilibrium which is instantaneously reestablished by a readjustment of the various thoracic viscera.

In order to understand better the mechanism of this readjustment, let us analyze it as it would occur in simple hypothetical cases. When both hemithoraces are exactly alike in capacity and both lungs are equally expanded to fill them, there would be comparatively little or no disturbance in the relative position of the mediastinum during inspiration. On the other hand, supposing one hemithorax to be relatively

immobile and the other hemithorax capable of large expansion, we can easily see how, during inspiration, a movable mediastinum would be shifted toward the larger hemithorax because of the rapidly increasing negative pressure developed therein. With both lungs filling their respective boxes, but one side of the thorax being larger than the other, but both mobile, we can easily conceive how the mediastinum would be displaced towards the side that expanded more. It would be aspirated, as it were, because of the larger negative pressure developing on the larger side during deep inspiration, a pressure which must be instantaneously balanced by an appropriate readjustment of the thoracic structures.

In the case under consideration, the mechanism of readjustment of the thoracic structures during inspiration is somewhat as follows: Both hemithoraces enlarge symmetrically. On the left, untreated side, this enlargement with its consequent rapidly developing increase in negative pressure is as rapidly compensated by the aspiration of air into the normally expanding lung. At the same time, on the pneumothorax side, because of the atelectasis of the collapsed lung, the aspiration of air into it is retarded and cannot possibly keep pace with the rapidly developing increment in the negative pressure. This uncompensated negative pressure on the pneumothorax side must be, and is, instantaneously balanced by the displacement, the sucking in, as it were, of the mediastinum toward that side.

As will be noted, the paradoxical movement of the diaphragm is not demonstrable in this case, because the most essential condition for its production—an inert diaphragm—is absent.

In summing up, the essential conditions for the production of the "pendular movement of the mediastinum" are two; First, a flexible mediastinum, that is, one relatively free from adhesions; second, a labile intrathoracic equilibrium. Of these two conditions, the second is commonly present in the average pneumothorax case. The variable factor is the presence of a flexible mediastinum, and it alone determines the presence or absence of the phenomenon. It should be added, however, that the extent of the pendular movement of the mediastinum will be largely determined by the intrapleural pressure on the pneumothorax side. In our own experience the best demonstrations were observed with a pressure of about  $-5$   $-3$  cm. of water.



*Case 2.* (Figures 3 and 4.) In these figures the paradoxical movement of the diaphragm is graphically illustrated. Figure 4 shows the position of the two halves of the diaphragm in deep inspiration and figure 3 shows these after a forced expiration. In this case the movement of balance was beautifully demonstrated radioscopically, but was only imperfectly radiographed. However, figures 5 and 6 show this in a striking manner.



FIGS. 3 AND 4. CASE 2

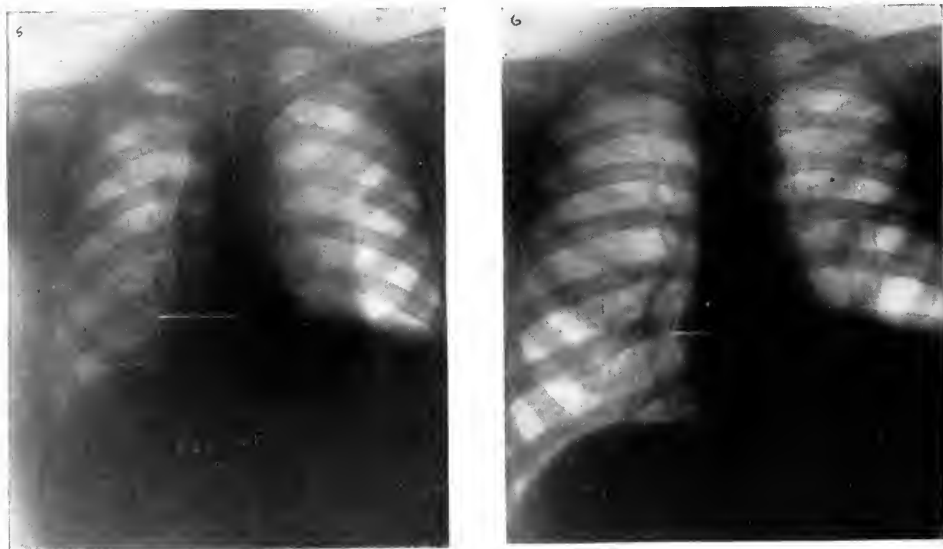
FIG. 3. Taken in forced expiration. Note small difference in height of fluid level on pneumothorax side and crest of diaphragm on untreated side.

FIG. 4. Taken in deep inspiration. Note increased difference between height of fluid level on pneumothorax side and crest of diaphragm on untreated side, thus showing "paradoxical movement of diaphragm." Pendular movement of mediastinum is also seen.

The mechanism of this phenomenon is not unlike the one traced in our discussion of the "pendular movement of the mediastinum." The essential condition here is an inert diaphragm easily affected by differences in pressure. To be inert and passive, it must be free from adhesions and paralyzed. This paralysis results from the suppression of the respiratory function of the lung, and from the presence of air or fluid in the pleural cavity, according to the law of Stokes (3). It is to be noted that the "pendular movement of the mediastinum" is not absent in this case because the mediastinum is not effectively fixed by adhesions.

*Case 3.* (Figures 5 and 6.) These two figures strikingly demonstrate both phenomena in the same patient. As the mechanism involved has been sufficiently discussed in connection with the first two cases, it need not be gone into again.

In this instance we have a flexible mediastinum, an inert diaphragm free from adhesions, and a labile intrathoracic equilibrium. These are



FIGS. 5 AND 6. CASE 3

FIG. 5. Taken in forced expiration. Note the long distance of right cardiac border from midsternal line and small difference in the height of the crest of diaphragm on untreated side and fluid level on pneumothorax side.

FIG. 6. Taken in deep inspiration. Note markedly diminished distance of right cardiac border from midsternal line; also even more marked increase in the difference of the height between the crest of diaphragm on the untreated side and the fluid level on the pneumothorax side. The "pendular movement of the mediastinum" and "paradoxical movement of the diaphragm" are both clearly shown.

the very conditions, and the only ones, necessary for the production of these phenomena which are best characterized as "movements of balance."

It is noteworthy that the presence of an effusion in the last two cases did not interfere with the production of the "movements of balance." The comparative rarity of these phenomena in pneumothorax cases, referred to by Barjon, is easily explained by the great frequency of

diaphragmatic and mediastinal adhesions in tuberculous chests; and it is, apparently, not due to the complexity of their mechanism.

In summing up, intrathoracic equilibrium in pneumothorax is constantly being disturbed and readjusted. A change in the intrathoracic pressure in the pneumothorax side must be balanced by appropriate changes in the untreated hemithorax and in the relative position of the mediastinal structures. The significant thing in the study of the mechanism of the so called "movements of balance" is that these movements are in response to a delicately adjusted and extremely labile intrathoracic equilibrium frequently existing in pneumothorax.

#### PRACTICAL INFERENCES

The practical significance of the effects of the disturbance in the intrathoracic equilibrium in pneumothorax should be thoroughly appreciated. However, it is not the purpose of this paper to discuss this phase of the subject in detail but merely to summarize the salient points.

In the presence of a fixed mediastinum, the effects on the untreated side are practically negligible, because the rigid mediastinum will stand the brunt of the increased intrathoracic pressure without transmitting it to the untreated side. In the presence of a flexible mediastinum (one practically free from adhesions) the increased intrathoracic pressure on the pneumothorax side will affect the intrathoracic pressure as well as the negative intrapleural pressure on the untreated side, increasing the one and decreasing the other. The extent of these influences will depend on the elastic recoil (flexibility) of the mediastinum and the pressure exerted from the pneumothorax side. In any event, there will, of necessity, result a partial compression of the untreated lung with resultant diminution in its air reserve, but with a proportionate increase in the ventilation of its alveoli. That this partial compression of the untreated side may have, and frequently does have, a beneficial effect has been well demonstrated. Many observers have recorded the great improvement in the affected untreated lung that has come about as a result of the pneumothorax on the opposite, more affected lung. Allowing for other factors which may have a share in it, we cannot help feeling that the partial compression of the untreated lung played no small part in this beneficial effect.

Another important influence of the increased intrathoracic pressure in pneumothorax is its effect on the circulatory apparatus. It diminishes or totally destroys the "aspiratory factor" in the venous circulation.

As is well known, the thoracic aspiration of the blood from the large veins into the right heart during inspiration is one of the important factors in the venous return. Such an interference with the aspiratory factor seriously embarrasses the venous return, thus favoring stasis or causing increased cardiac action to compensate for this embarrassment.

It is also to be noted that the displacement of the thoracic viscera resulting from changes in the intrathoracic pressure relationship may mechanically interfere with their functional efficiency; and, when occurring suddenly, may give rise to distressing symptoms and even result fatally if not quickly relieved. The most dramatic illustration of the effects of sudden disturbance in the intrathoracic equilibrium is not infrequently observed during aspiration of effusions whether it be in pneumothorax cases or in other instances of copious exudates. A typical instance is the following:

Case 2 was being aspirated. While the fluid was being cautiously and slowly withdrawn, the patient's pulse and general condition were carefully observed. He was also instructed to inform the operator at once the moment he felt "queer" in the chest. When about 1000 cc. of fluid were withdrawn, the patient suddenly began to complain of extreme precordial distress and, as he subsequently explained, he thought he was dying. His pulse and general appearance showed marked cardiorespiratory embarrassment. The aspiration was stopped immediately, and air was allowed to flow in rapidly, all connections with the pneumothorax apparatus having been previously arranged, as is done in all our aspirations. In less than a minute these distressing symptoms were relieved completely as a result of the rapid reestablishment of the intrathoracic equilibrium by recreating the pressure conditions which existed in the thorax prior to the aspiration. Similar instances can be cited from the pneumothorax experience of all operators.

#### SUMMARY

1. The effects of the changed intrathoracic condition in pneumothorax on the untreated side and on the circulatory apparatus are far-reaching. Therefore, the mechanism of the intrathoracic equilibrium in pneumothorax should be thoroughly understood by the operator.

2. With a mediastinum effectively fixed by adhesions, the effect of unilateral pneumothorax on the opposite side is practically negligible. For the rigid mediastinum will stand the brunt of the increased intrathoracic pressure on the pneumothorax side without transmitting it to the untreated side.

3. In the presence of a flexible mediastinum the intrathoracic equilibrium in pneumothorax is very delicately adjusted. And any disturbance in the intrathoracic pressure on the treated side will have a proportionate effect on the intrathoracic pressure on the untreated side, as well as produce a readjustment in the position of the mediastinal structures.

4. The "paradoxical movement of the diaphragm" and the "pendular movement of the mediastinum" are phenomena frequently observed in radioscopic study of pneumothorax. These are better characterized as "movements of balance," and are in response to a delicately adjusted, constantly changing, and extremely labile intrathoracic equilibrium frequently existing in pneumothorax under the following conditions: (a) flexible mediastinum, that is, one relatively free from adhesions, and (b) inert diaphragm, that is, one free from adhesions and paralyzed.

5. The practical significance of the effects resulting from the disturbance in the intrathoracic equilibrium in pneumothorax are as follows:

*a. Effects on the untreated side:* In the presence of a flexible mediastinum, there will result a decrease in the size of the untreated hemithorax, with a corresponding compression of the untreated lung. This partial compression of the untreated lung may be of benefit in cases of bilateral involvement.

*b. Effect on the circulatory system:* An increase in the intrathoracic pressure diminishes or totally abolishes one of the most important factors of the venous circulation, namely, the thoracic aspiration of the blood from the large veins into the right heart during inspiration. Such interference seriously embarrasses the venous return, thus favoring stasis or causing increased cardiac burden to compensate for this embarrassment.

*c.* That sudden disturbance of the intrathoracic equilibrium may result in serious, and often fatal, cardiorespiratory embarrassment, is illustrated by incidents frequently occurring during aspiration of cases of hydropneumothorax. That the distressing symptoms resulting from such sudden disturbances are quickly relieved by reestablishment of the preëxisting equilibrium is particularly noteworthy.

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## TORUS PALATINUS

### AN ALLEGED NEW SIGN OF PULMONARY HYPERTROPHIC OSTEOARTHROPATHY

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Nearly a century ago Chassaignac (1) described, probably for the first time, a protrusion in the midline of the hard palate as *exostose médio-palatine* and looked upon it, mistakenly as we know, as a pathognomonic sign of syphilis.

Over seventy years ago Carabelli (2) wrote that in rare cases there is found in the line of junction of the processes of the palate bone a considerable protrusion which extends either along its whole length or is confined to the middle of the palate in the form and length of half a pigeon's egg. He termed it *torus palatinus*, and states that it is peculiar that this anomaly occurs in most if not all the members of certain families, adding, "I find it most necessary to call attention to it because, since very little has been known about it until now, it could be looked upon and treated as the product of a disease."

The great anatomist and anthropologist, Hyrtl (3), states that it occurs as "an unimportant, harmless convexity of the roof of the mouth in completely healthy persons."

Torus palatinus has received a great deal more attention from anthropologists and students of mental and nervous diseases than from pathologists and clinicians. Along with innumerable other abnormalities it has been looked upon as a sign of degeneracy in the sense of Lombroso.

Among the more prominent authorities who have made a study of the torus palatinus may be mentioned Stieda (4), who wrote a monograph on it, Sommer (5), Berkhan (6), who found it occasionally in stutterers and gives a schematic and cross section illustration of it, Calori (7), Waldeyer (8) and Kurella (9).

Näcke (10) devotes a chapter to an exhaustive discussion of the condition. He divides torus palatinus, according to shape, into four dis-

tinct and one mixed variety, and was the first to study its incidence in a large series of living cases. In 1449 normal and psychopathic individuals he found it present in 21.9 per cent. Of these, 1179 were



FIG. 1. PHOTOGRAPH, SHOWING VERY LARGE TORUS PALATINUS



FIG. 2. PHOTOGRAPH, SHOWING DEPRESSION IN UPPER DENTAL PLATE OF SAME PATIENT

females with an incidence of 23.6 per cent, and 270 males with 14.4 per cent. The mentally diseased women, including epileptics, idiots and criminals, showed an incidence of 23.9 per cent and the healthy women of 22.7 per cent. The analogous classes of men showed 15.5 per cent and 13.6 per cent respectively. Although he found it most frequently in



epileptic women (32.9 per cent) and female criminals (34.4 per cent), it is extremely doubtful from the general figures that any importance can be attached to it as a stigma of degeneracy.

Stieda found the torus in 35.1 per cent of both sexes. He examined 1500 skulls of Prussians, Armenians, Africans, Frenchmen, Russians and Asiatics, and concluded that the torus has no anthropological significance and marks no racial distinction (11).

Näcke believes that an instance of its occurrence in prehistoric man is to be found in Hamy's (12) description of a superior maxilla found in the Grotto of Gourdan.

The torus has been found in embryos. It probably arises *in utero* or shortly after birth, and has not been known to develop in adults.

Schmidt (13) states that the torus occasionally reaches a considerable size and has no pathological significance.

Recently Corper and his co-workers (14), in an investigation of 102 consumptives and 12 normal individuals, have described this protrusion in the midline of the hard palate as one of the manifestations of hypertrophic osteoarthropathy in pulmonary tuberculosis, with a greater incidence in active cases and in females. It appears from their study that it was unknown to them that this anomaly had been extensively described under the name of *torus palatinus* and that it has been correlated with other pathological conditions.

In order to determine whether torus palatinus has any relation to hypertrophic osteoarthropathy, we examined the patients in the Tuberculosis Division of Montefiore Hospital and Bedford Sanatorium, a material of the same ethnic grouping as that of Corper. The great majority are active and quiescent, moderately and far advanced cases, varying in age from eighteen to sixty-eight years and in duration of disease from one to thirty years.

Of 269 cases (147 males and 122 females) 42, or 15.6 per cent, presented a protuberance along the palatine suture, varying considerably in size and shape. Only a few cases of the size of half a pigeon's egg were found. Of the females 25, or 20.6 per cent, and of the males 17, or 11.6 per cent, presented a torus. We have classified the approximate gradations in size of the protuberance as slight, moderate and marked (table 1).

Only 7 cases with a torus showed clubbing of the fingers and toes and hyperconvexity of the nails, singly or in one or another combination. Slight clubbing of the fingers was associated in 3, and slight to moderate hyperconvexity of the nails in 6 cases. In only 1 was the hypercon-

vexity marked. Combined clubbing and hyperconvexity occurred in only three. Clubbing of the toes was present to a slight degree in 2, slight hyperconvexity in 3, moderate in 2, marked in 1 and in only 1 case was it combined.

The most marked cases of clubbing of the fingers and toes and hyperconvexity of the nails did not exhibit a torus, while only 3 of the 20 moderate and none of the 7 marked instances of the torus showed clubbing or hyperconvexity. Two cases in which the torus reached its most extreme size showed typical tapering fingers and no signs whatsoever of hypertrophic osteoarthropathy. Thickening of the carpal and metacarpal bones and of the corresponding bones of the feet, or enlargement of the lower ends of the humerus and femur or abnormal prominence of the malar bones, some of the most cardinal signs of hypertrophic osteoarthropathy, were entirely absent in all of our cases of torus.

TABLE 1

*Incidence of torus palatinus in two hundred and sixty-nine cases of pulmonary tuberculosis*

SEX	NUMBER OF CASES	NUMBER WITH TORUS PALATINUS	PER CENT	SLIGHT	MODERATE	MARKED
Males.....	147	17	11.6	8	7	2
Females.....	122	25	20.5	7	13	5
Total.....	269	42	15.6	15	20	7

Ridging of the nails occurred in many of our cases; but, since our subsequent examination revealed a similar incidence of this condition in other chronic diseases, we could not permit ourselves to regard it as a manifestation of hypertrophic osteoarthropathy, and hence have omitted mention of its concomitance with torus palatinus.

No relation of the torus to the activity of the disease, its duration nor to the age of the patient could be established.

If torus palatinus were a manifestation of hypertrophic osteoarthropathy, we should expect its incidence to be greater in males among whom Marie's disease is known to occur more frequently, in the proportion of nearly 8 to 1(15). As a matter of fact, our results, in agreement with those of other observers, show that torus palatinus predominates in females, in whom also its most marked degrees are found.

Hypertrophic osteoarthropathy is secondary in the great majority of cases to chronic pulmonary and pleural diseases. Janeway (16) found

it thus associated in 65 of 93 cases, and Locke (17) in 113 of 144. It occurs most frequently in pulmonary tuberculosis, especially with cavity formation, although it is probable that even here bronchiectasis, which is considered by some as the most frequent pathological process causing it, is the underlying factor. Bonney (18) claims that it is extremely rare in pulmonary tuberculosis. It has occasionally been found associated with other diseases. Its etiology is obscure, but it is probably due to toxic absorption of an uncertain character and venous stasis, singly or combined (19).

Clubbed fingers are nowise characteristic of pulmonary tuberculosis uncomplicated by bronchitis and bronchiectasis, but occur in far more pronounced degrees in other pulmonary and cardiac diseases associated with dyspnea and cyanosis. Tapering fingers are probably more characteristic of phthisis, and hyperconvexity of the nails is considerably more common.

Some authorities are inclined to make a distinction between simple clubbing and that associated with hypertrophic osteoarthropathy. Fishberg (20) says that the latter is distinguished clinically by involvement of the wrists, and usually also of the feet, and decided curvature of the spine in most cases, in addition to clubbed fingers. He also finds that in simple clubbing, such as found in phthisis, the deformity is due to hypertrophy of the soft parts, and apparently not to any changes in the bones and joints. Others look upon simple clubbing as an incipient or arrested stage of the disease (21). Lord (19) states, "The clubbing of the fingers is due to a swelling of the soft parts and not to bony enlargement, both in simple clubbing and that associated with Marie's disease."

We therefore believe that the clubbing of the fingers and toes in our cases of torus palatinus in pulmonary tuberculosis need not necessarily be looked upon as an expression of hypertrophic osteoarthropathy. On account of this, and the approximately equal incidence of the torus in an extremely varied clinical material (see below), without signs of hypertrophic osteoarthropathy, we did not consider it of importance to determine the presence or absence of bony or articular changes by radioscopic examination.

In order to ascertain the incidence of torus palatinus in conditions other than pulmonary tuberculosis we examined the large and unusual material in the other divisions of Montefiore Hospital.

Three hundred and eighty-six patients (196 males, 160 females, 20 boys and 10 girls) in the medical, neurological, orthopedic and cancer services revealed 74 (19.2 per cent) cases of torus. Thirty-nine, or 23 per cent, were females and 35, or 16.2 per cent, were males, of all ages.

Through the courtesy of Dr. V. P. Gibney, Surgeon in Chief of the Hospital for Ruptured and Crippled, we had the privilege of examining 84 children and 57 adults in that institution. Of the former, 15, or 17.8 per cent (10 girls and 5 boys), and of the latter 11, or 19.3 per cent (6 males and 5 females), presented a torus.

Of the total number of individuals examined, 116 were children with an incidence of the torus palatinus in 18, or 15.5 per cent, and 680 adults with 124, or 18.2 per cent. It would therefore appear that torus palatinus is not a development of adult life. It is furthermore important to note that a considerable number of our cases, particularly those from the Hospital for Ruptured and Crippled is such that hypertrophic osteoarthropathy, as a result of toxic absorption or venous stasis, may be excluded.

The extremely varied diseases and conditions (tables 2 and 3) in which the torus palatinus was present does not permit its correlation with any one pathological process. Although hypertrophic osteoarthropathy has been found coincident with such conditions as valvular cardiac disease, carcinoma, sarcoma and a few other conditions, in which the cause of the association cannot be explained, no evidences of it were present in our cases of torus palatinus. Neither the cardiacs, nor the cases of chronic bronchitis and bronchiectasis, of bronchial asthma and neoplasm of the lung, which presented a torus, showed clubbing of the fingers, curving of the nails or any other signs of Marie's disease.

If we combine the three groups we find that in a total of 796 cases varying degrees of the torus palatinus were present in 142, or approximately 18 per cent: 79 were females and 63 males (table 4).

We have found that inspection is sufficient to reveal the presence of a torus. Palpation is unpleasant both to the patient and the examiner and does not give more exact information.

In none of our cases of even the most marked degrees had there been at any time a knowledge of its presence by the patient nor was there any interference with speech and enunciation.

TABLE 2

*Seventy-four cases of torus palatinus in diseases other than pulmonary tuberculosis*

	SLIGHT		MODERATE		MARKED	
	Male	Female	Male	Female	Male	Female
<i>Neurological</i>						
Multiple sclerosis.....	3	2	1	0	0	0
Paralysis agitans.....	0	3	0	0	0	0
Hysteria.....	0	1	1	1	0	0
Tumor of the spinal cord.....	1	0	0	0	0	1
Tabes dorsalis.....	0	1	1	0	0	0
Muscular dystrophy.....	1	0	1	0	0	0
Neurasthenia.....	0	1	0	0	0	0
Aniyotrophic lateral sclerosis.....	0	1	0	0	0	0
Multiple neuritis.....	1	0	0	0	0	0
Cerebellar neoplasm.....	1	0	0	0	0	0
Hemiplegia, adhesive pleurisy.....	0	0	1	0	0	0
Psycho-neurasthenia.....	0	0	0	0	1	0
Pseudomuscular hypertrophy.....	1	0	0	0	0	0
<i>Medical</i>						
Cardiac, cardio-nephritic, arteriosclerosis..	3	3	1	3	0	0
Arteriosclerosis with hemiplegia.....	1	4	1	0	0	0
Thrombo-angitis obliterans.....	2	0	1	1	0	0
Chronic osteomyelitis, mitral stenosis....	1	0	0	0	0	0
Mediastinal Hodgkin's, pulmonary tubercu- culosis.....	0	0	0	1	0	0
Fracture of femur, pulmonary tuberculosis	0	0	0	1	0	0
Diabetes mellitus.....	0	0	1	0	0	0
Diabetes mellitus, cardio-nephritis.....	0	0	1	0	0	0
Chronic bronchitis, bronchiectasis.....	1	0	0	0	0	0
Neoplasm of lung.....	1	0	0	0	0	0
Pituitary disease, obesity.....	1	0	0	0	0	0
Lutetic aortitis.....	1	0	0	0	0	0
Bronchial asthma.....	0	0	0	0	0	1
Pernicious anemia.....	0	0	0	1	0	0
Unclassified.....	1	0	0	0	0	0
<i>Orthopedic</i>						
Polyarthritis deformans.....	0	1	0	2	0	3
Infectious polyarthritis.....	1	0	0	1	0	0
Chronic multiple proliferative arthritis....	1	0	0	0	0	0
Polyarthritis deformans, lues.....	0	0	0	1	0	0
Arthritis of knee joints.....	0	1	0	0	0	0
<i>Skin and cancer</i>						
Chronic pemphigus.....	1	0	0	0	0	0
Scleroderma.....	0	1	0	0	0	0
Carcinoma of stomach.....	0	2	0	0	0	0
Carcinoma of uterus and adnexa.....	0	0	0	1	0	0
Carcinoma of rectum.....	1	0	0	0	0	0
Total.....	24	21	10	13	1	5

TABLE 3

*Fifteen cases of torus palatinus in eighty-four children and eleven cases in fifty-seven adults from the Hospital for Ruptured and Crippled*

	SLIGHT		MODERATE		MARKED	
	Male	Female	Male	Female	Male	Female
<i>Children</i>						
Congenital dislocation of hip.....	2	1	0	2	0	0
Sequellae of anterior poliomyelitis.....	0	0	0	4	0	0
Curvature of spine.....	1	0	0	0	0	0
Hernia.....	0	1	0	0	0	0
Abscess of foot.....	0	0	1	0	0	0
Osteomyelitis.....	0	0	0	0	0	1
Tuberculous hip disease.....	0	0	1	1	0	0
Total.....	3	2	2	7	0	1
<i>Adults</i>						
Hernia.....	0	0	1	1	0	0
Sarcoma of thigh.....	0	0	0	0	1	0
Liposarcoma of nasopharynx.....	0	0	1	0	0	0
Multiple arthritis.....	0	0	1	0	0	0
Arthritis of knee.....	0	0	0	1	0	0
Arthritis of hip.....	0	0	0	0	0	1
Contractures.....	0	0	0	0	0	1
Hallux valgus.....	0	0	0	0	0	1
Tuberculosis of knee.....	1	0	0	0	0	0
Tuberculosis of spine.....	1	0	0	0	0	0
Total.....	2	0	3	2	1	3

TABLE 4

*Summary of one hundred and forty-two cases of torus palatinus in seven hundred and ninety-six cases*

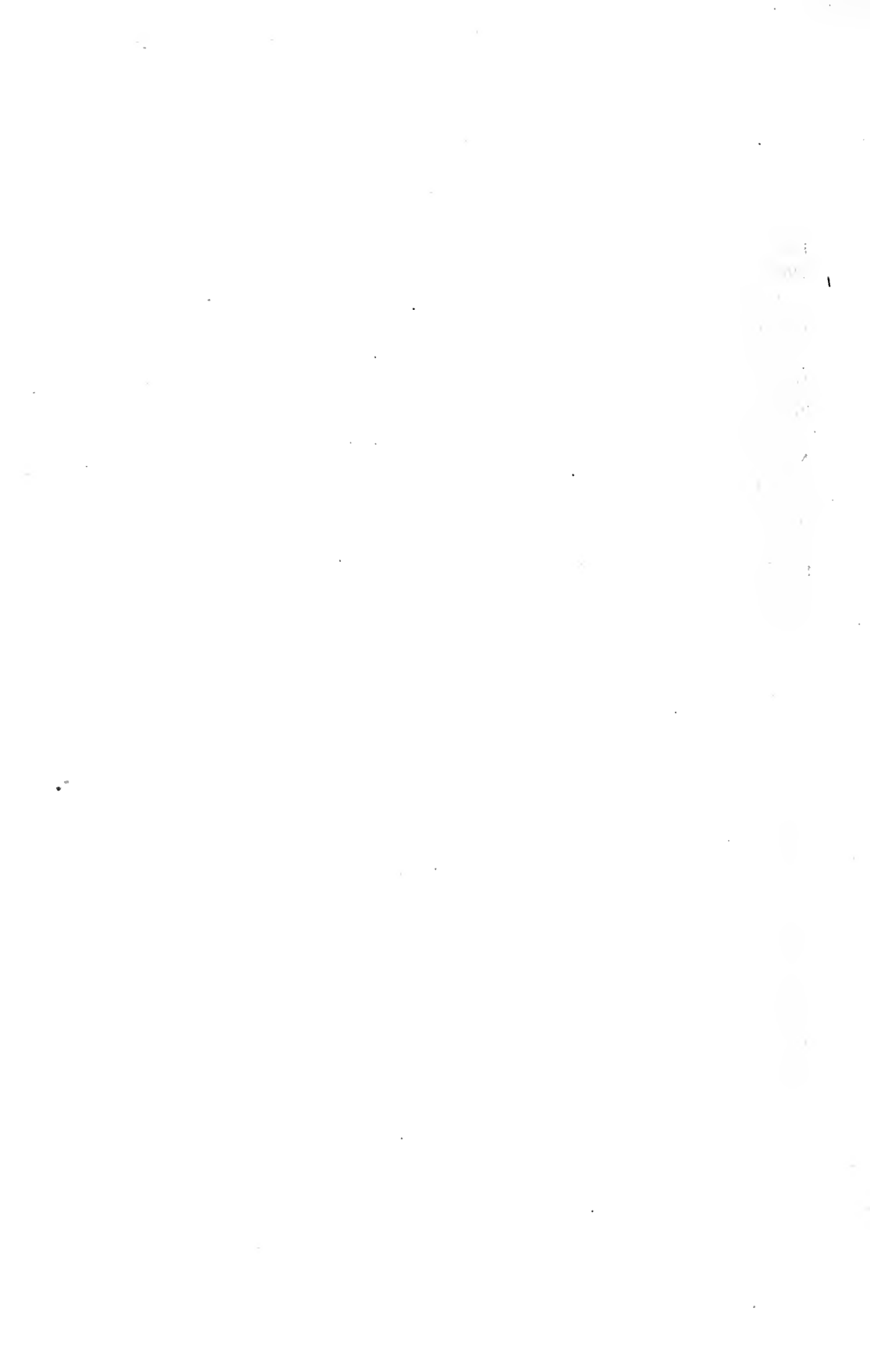
SEX	NUMBER OF CASES	NUMBER WITH TORUS PALATINUS	PER CENT	SLIGHT	MODERATE	MARKED
Males.....	363	52	14.3	32	17	3
Females.....	292	64	21.9	28	26	10
Total.....	655	116	17.7	60	43	13
<i>From Hospital for Ruptured and Crippled</i>						
Males.....	141	11	18.4	5	5	1
Females.....		15		2	9	4
Grand total.....	796	142	17.8	67	57	18

## CONCLUSIONS

1. A protuberance of varying size and shape in the midline of the hard palate and termed *torus palatinus* occurred in 18 per cent of a series of 796 cases of various diseases and conditions.
2. We do not find any convincing data for assuming that it is of any importance as a stigma of degeneracy.
3. There is no evidence whatever that it is a manifestation of hypertrophic pulmonary osteoarthropathy, or that it can be correlated with any disease.
4. It has a greater incidence and is of more marked degree in females. No explanation for this can be offered.
5. It occurs with approximately the same frequency in children and in adults.
6. Nothing definite about its etiology is known. It is said to be due to disturbances of nutrition of obscure origin in embryonic and fetal life or shortly after birth (rachitic?).
7. It is probably always congenital and of no pathological significance.

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**COMPARATIVE PROGNOSIS IN TUBERCULOUS LESIONS  
OF THE RIGHT AND LEFT LUNG. A STUDY OF  
1048 CASES.**

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VERY few, and somewhat conflicting, are the recorded observations on the comparative prognosis of right- and left-sided tuberculous lesions and bilateral lesions in which one lung is more extensively involved. Brown<sup>1</sup> maintains that there is no difference in gravity between lesions of the right and the left lung. On the other hand, other observers speak of the mildness of right-side lesions in comparison with those of the left side, and point to the less favorable prognosis in lesions of the left lung. Text-books on the subject shed but little light on this phase of pulmonary tuberculosis, and references to such investigations cannot be found in most standard works on disease of the lungs. It is evident, therefore, that this subject will stand further investigation.

In reviewing the extensive literature on therapeutic pneumothorax one is impressed with the fact that the number of left lungs collapsed is far greater than that of the right, notwithstanding that, generally considered, the left lung is less frequently involved in pulmonary tuberculosis. This would indicate a greater frequency of severe lesions in the left lung. Impressed with this occurrence, Tecon and Aimard,<sup>2</sup> Mark<sup>3</sup> and others have carefully analyzed the data at their disposal. They conclude that as the disease advances there is a great preponderance of left-side lesions, and that a tuberculous condition in the left lung is of more serious import than one in the right and demands a more guarded prognosis. Mayer,<sup>4</sup> Cavalcanti,<sup>5</sup> Strandgaard<sup>6</sup> and others, although unable to confirm the above observation as regard the much greater frequency of left-lung involvements in the advanced stages of

phthisis, agree, nevertheless, that the prognosis is less favorable in those whose predominating lesion is in the left lung.

The 1048 cases which form the basis of this communication were observed for from five months to several years. They were all subjected to repeated roentgenological examinations, and their diagnosis was clear cut. The classification of the National Tuberculosis Association was strictly adhered to, both in regard to diagnosis on admission and condition on discharge.

TABLE I.—LUNG INVOLVEMENTS IN 1048 CASES

Right lung only.	Left lung only.	Both lungs.	
		Right lung most.	Left lung most.
326, or 31.1 per cent	152, or 14.5 per cent	344, or 32.8 per cent	226, or 21.6 per cent

The figures of Table I show that of the 1048 cases studied, 152, or 14.5 per cent, suffered from tuberculosis of the left lung only and 226 from bilateral pulmonary tuberculosis with preponderating left-side involvement, or a total of 36.1 per cent of preponderating left-lung lesions; while 326, or 31.1 per cent, suffered from right-side lesions only, and 344, or 32.8 per cent, were afflicted with bilateral lesions in which the right side was more extensively involved; or a total of preponderating lesions of the right lung of 63.9 per cent. In other words, in unilateral lesions, the percentage of right-side involvement was about 2 to 1 as compared with the left, while in bilateral lesions there was a decided increase in the number of involvements of the left lung, so that the percentage of preponderating right-side lesions was only 3 to 2 as compared with the left.

TABLE II.—LUNG INVOLVEMENTS IN THE VARIOUS STAGES OF PHTHISIS.

		Right.		Left.	
		No.	Per cent.	No.	Per cent.
Stage I	Male . . . . .	125	11.9	53	5.0
	Female . . . . .	70	6.7	44	4.2
Stage II	Male . . . . .	213	20.3	93	8.9
	Female . . . . .	115	11.1	60	5.8
Stage III	Male . . . . .	92	8.8	69	6.5
	Female . . . . .	55	5.1	59	5.7
Total . . . . .		670	63.9	378	36.1

Considering the various stages of the disease separately, Table II discloses the interesting fact that whereas in the first and second stage of the disease the percentage of the right-side lesions is about 2 to 1 as compared to the left side, the percentage of the right involvements in the third stage is not greater, but is about equal to that of the left. This is not in agreement with the figures of Tecon, Aimard and Mark, which show that in advanced phthisis the left side is much more often involved than the right. The evidence, however, points to a remarkable increase in the number of left-side lesions as the disease advanced.

TABLE III.—RELATION OF SIDE OF LESION TO ACTIVITY OF DISEASE.

	Male.				Female.			
	Right.		Left.		Right.		Left.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Inactive . . .	285	66.3	119	56.8	128	53.4	57	41.2
Active . . .	145	33.7	96	43.2	112	46.6	96	58.8

Analysis of Table III shows that both male and female patients in all stages of the disease whose preponderating lesion was on the left side ran an active course while at the sanatorium, more frequently than those with preponderating right-side lesion, the ratio being 4 to 3 in favor of the left lung.

TABLE IV.—CONDITION ON DISCHARGE.

		Male.				Female.			
		Right.		Left.		Right.		Left.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Stage I	Arrested; improved . .	121	96.8	52	98.1	67	95.7	42	95.5
	Unimproved; progressive .	4	3.2	1	1.9	3	4.3	2	4.5
Stage II	Arrested; improved . .	176	87.4	80	86.0	95	82.6	48	80.0
	Unimproved; progressive .	37	12.6	13	14.0	20	17.4	12	20.0
Stage III	Arrested; improved .	52	56.5	27	39.2	34	61.8	28	47.5
	Unimproved progressive	40	43.5	42	60.8	21	38.2	31	52.5
Total . . .		430		215		240		163	

Scrutiny of the figures in Table IV discloses the fact that in early tuberculosis the prognosis is no better in right than in left apical lesions. However as the disease advances the prognosis becomes less favorable in predominating lesions of the left lung. Thus the percentage of patients discharged "unimproved" and "progressive" in the second stage in male patients is 14 per cent in predominating left-lung lesions as against 12.6 per cent with right-lung involvements, and in the females 20 per cent "progressive" in lesions of the left lung as compared with 17.4 per cent in predominating right-lung lesions. In the third stage the prognosis in left-side lesions seems to be decidedly worse than in lesions of the right lung. Here the percentage of patients discharged with condition "progressive" is 60.8 per cent in left predominating lesions as compared with 43.5 per cent in right predominating lesions among the males and 52.5 per cent "progressive" in lesions of the left lung as compared with 38.2 per cent in right-side lesions among the females, or a ratio of 3 to 2 among males and 4 to 3 among females.

**Discussion.** Although it is universally admitted that the minimal lesion in pulmonary tuberculosis is most frequently found at the right apex the available data do not indicate the exact proportion of right and left apical involvements. This proportion varies within a wide range, depending on the character of the investigation. There is, however, a fair agreement that as the disease advances there is a decided increase in the number of left-lung lesions, so that when we observe a group of patients in whom the disease has reached the so-called "third stage" we find that in cases with unilateral disease the left lung is involved as often as the right, and in cases with bilateral lesions the predominating lesion is discerned on the left side no less frequently than on the right. This in itself, however, does not shed much light on the relative prognosis in lesions of either side. When, on the other hand, we look into the results of institutional treatment in all stages of phthisis we gain a definite idea as to the relative prognosis of right- and left-side lesions. Our observations are in accord with most observers, to the effect that the prognosis in early right apical lesions is no better than in lesions of the left apex. It is quite different, however, in the advanced stages of phthisis. Here it is definite that the prognosis is less favorable in cases with predominating lesions of the left lung. These patients are liable to run an active course more often than those with preponderating right-side lesions, and the percentage of these cases discharged "unimproved" and "progressive" is almost one and one-half times as large as that of cases with right-side involvement.

There seems to be some conflict of opinion as to the probable explanation of the increased gravity in left-side lesions. It is stated that the narrow caliber of the left bronchus, by interfering with the proper aëration of the left lung, favors the rapid progress

of the disease once it is implanted in its upper lobe. This explanation, however, does not seem to possess the germ of conviction.

A more rational explanation for the greater gravity in left-side lesions is to be found in this: The right lung has three lobes whereas the left lung has but two. The division of the lung into lobes seems to retard the rapid spread of tuberculosis because the fissures which separate the lobes are lined with double layers of serous membranes which are more refractory to tuberculous disease than the lung tissue proper. It is evident that the right lung with two fissures is better equipped to check the rapid spread of the disease than the left, which, after the one fissure is passed, has no other barrier to retard the spread of the disease.

It has recently been pointed out that even in health, areas of atelectasis are frequently found in the left lower lobe. These are probably caused by the encroachment of the pericardium and its contents on the left lower lobe and are responsible for the marginal rales which are so often heard in the region of the left base. Sewall<sup>7</sup> states that "a conclusion might be plausible that the atelectatic condition distinctly favors the development of phthisis." Is it not possible that, at least to some extent, atelectasis favors the rapid spread of tuberculosis in the left lung?

There are also causes which indirectly render the prognosis of lesions on the left side more serious. Clinicians have long recognized that patients suffering from phthisis stand the dislocation of the mediastinal organs to the right much better than their dislocation to the left. Dyspnea, cyanosis, palpitation, etc., are not often complained of in acquired dextrocardia due to fibrosis and shrinkage of the right lung, whereas the above symptoms are often met with in a distressing form in patients with sinistracardia due to advanced tuberculosis of the left lung. We see many cases with extreme dextrocardia who work and do well generally for many years, but those whose cardiac displacement is to the left have but a small cardiac reserve and seldom do well.

Shrinkage of the left lung also causes marked retraction of the left diaphragm and adjacent abdominal viscera. In some instances the retraction is so extreme that the stomach is actually pulled into the thoracic cavity and simulates a diaphragmatic hernia or localized pneumothorax.<sup>8</sup> The normal function of the stomach is thus materially interfered with to a much greater extent than is possible in lesions of the right side, no matter how extensive. This further aggravates the prognosis in advanced disease of the left lung.

**Summary.** The results of our study lead us to conclude:

1. In early tuberculosis the right side is affected twice as often as the left.
2. As the disease progresses there is a marked increase in the number of involvements of the left lung, so that in the advanced

stage of the disease the right and the left lungs are numerically equally involved.

3. Patients with a predominating left-lung involvement are liable to run an active course more often than those with preponderating right-side lesions.

4. In early phthisis the side of the lung involved has no definite relation to the general prognosis.

5. In advanced phthisis the prognosis is distinctly less favorable in those with preponderating lesions of the left lung.

6. The presence of but one interlobar fissure, moderate atelectasis and the evil effects of sinistracardia and retraction of the stomach are factors which contribute toward the greater gravity of left-lung lesions as compared to the right.

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# CLINICAL SIGNIFICANCE OF ALTERED INTRATHORACIC EQUILIBRIUM IN PNEUMOTHORAX

WITH SPECIAL REFERENCE TO OPTIMAL PRESSURES \*

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In a recent publication entitled "Intrathoracic Equilibrium in Pneumothorax,"<sup>1</sup> we discussed in some detail the mechanics and dynamics of this problem. In the present communication we purpose to restate as briefly as possible the fundamental ideas of the earlier contribution and to discuss in some detail the other phase of the subject, namely, the clinical effects of the altered intrathoracic equilibrium in pneumothorax.

Graham and Bell<sup>2</sup> touched the heart of the subject, when they came to the conclusion that: "From the standpoint of pressure relations, the thorax may be considered as one cavity instead of two. Any change in pressure in one pleural cavity will affect also the other one almost equally. The common conception of collapsed lung on one side and 'healthy' or 'normal' lung on the other in the condition of open pneumothorax in the otherwise normal chest must be erroneous." This, they prove, applies as well to closed pneumothorax in chests relatively free from adhesions.

This fundamental conception has been corroborated by Simon<sup>3</sup> and Betchov,<sup>4</sup> in their experimental studies

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\* From the Montefiore Country Sanatorium.

<sup>1</sup> Read before the Clinical Section of the Eighteenth Annual Meeting of the National Tuberculosis Association, Washington, D. C., May 4, 1922.

1. Stivelman, B. P.; Hennell, Herman, and Golembe, Harry: *Am Rev. Tuberc.* **6**: 95 (April) 1922.

2. Graham, E. A., and Bell, R. D.: *Am. J. M. Sc.* **156**: 839 (Dec.) 1918.

3. Simon, S.: *Am. Rev. Tuberc.* **5**: 620 (Oct.) 1921.

4. Betchov, N.: *Schweiz. med. Wchnschr.* **51**: 43 (Oct. 27) 1921.

on the effect of pneumothorax on the pressure conditions in the untreated side in men and laboratory animals; and the results of our own experiments in a small but carefully studied series of rabbits also support this view.

Clinically, the phenomenon of the so-called "movements of balance" (i. e., the inspiratory displacement of the mediastinum toward the pneumothorax side and the paradoxical movement of the diaphragm) are perhaps the best illustrations of the delicacy with which the intrathoracic equilibrium is adjusted in pneumothorax in the presence of a flexible mediastinum and an inert diaphragm.

Our conclusions were: In the presence of a flexible mediastinum, the intrathoracic equilibrium in pneumothorax is very delicately adjusted, and any disturbance in the intrathoracic pressure on the treated side will have a proportionate effect on the intrathoracic pressure on the untreated side as well as produce a readjustment in the position of the mediastinal structures. On the other hand, with a mediastinum effectively fixed by adhesions, the effect of unilateral pneumothorax on the opposite side is practically negligible, for the rigid mediastinum will stand the brunt of the increased intrathoracic pressure on the pneumothorax side without transmitting it to the untreated side.

Bearing these fundamental principles of pneumodynamics in mind, we may now consider the clinical effects of the altered intrathoracic equilibrium in pneumothorax.

It is apparent that when the pneumothorax is localized by extensive adhesions, or the mediastinum effectively fixed, or both, high positive intrapleural pressure, even up to between 40 and 50 mm. of mercury, will cause no appreciable effect on the pressure conditions of the opposite side or the size and function of the untreated lung. Under such circumstances, as high pressure as can be borne in the particular case may be given in the presence of a therapeutic indication.

Such an indication exists particularly in cases in which the symptoms and signs point to a tendency toward obliteration of the pleural cavity, whether or not this occurs as a result of a complicating hydropneumothorax. Experience has taught us that such pleural

obliteration can be avoided in some cases and delayed in others by the judicious recourse to gradually increasing positive intrapleural tension. Unless this procedure is resorted to in these cases, a loss of pneumothorax will occur and the affected lung will rapidly reexpand, laying open the diseased foci and excavations, for the very relief of which the lung was collapsed. The danger of this reexpansion is particularly great because, once lost control of and given a chance to progress, pleural obliteration will preclude the possibility of resuming successful collapse therapy. It is unfortunate, indeed, that in some of these cases the pressure cannot be raised high enough because the gas under pressure escapes through the needle puncture into the adjoining and often surrounding subcutaneous tissue. And while a positive pressure of from 30 to 50 mm. of mercury may occasionally cause some adhesions to rupture, this unfortunate occurrence is not frequent enough to warrant an abandonment of this procedure in most cases.

It is different in the case of a flexible and labile mediastinum. Here increased intrapleural pressure on the pneumothorax side means not only proportionate increase of pressure on the opposite side but also a definite compression of the untreated lung. With one lung collapsed and the untreated lung somewhat involved, as it usually is in many cases subjected to collapse therapy, every effort should be made to embarrass as little as possible the untreated organ, which is now forced to perform the function of respiration practically unaided. Many of our failures in pneumothorax are, no doubt, due to the reactivation of tuberculous foci in the untreated lung, and might have been avoided by a more thorough appreciation of the pneumodynamics involved.

In these cases of bilateral involvement we must endeavor by patient observation to determine the amount of compression which the untreated lung can stand as a result of the increased intrapleural pressure on the treated side. Indeed, this is the most difficult problem to solve in cases that fall in this category.

Those who are most competent to judge have long realized that there is no such thing as a standard optimal pressure, even in the simpler pneumothorax

cases. Each patient is a law unto himself. A pressure which is sufficient to bring about an arrest of the disease in one case may be distinctly injurious in another. At one time we aimed to establish a positive pressure of about 4 cm. of water at the fourth inflation in all cases. We know of a patient who would have lost his life as a result of a telephone order to induce a positive pressure of 4 cm. had it not been for the quick action of the assistant, who, realizing the distress of the patient, withdrew some air by using the simple expedient of lowering the gas reservoir, i. e., reversing the siphonage until the patient was relieved. No dogmatic statements are possible, although it is generally observed that the best results are more frequently obtained when the intrapleural tension can be maintained at about — 2 to — 3 cm. of water. In such cases the affected lung is usually effectively collapsed and the untreated lung, by virtue of the flexible and labile mediastinum, is but lightly compressed.

Evidence is accumulating to the effect that this light compression of the so-called untreated but somewhat diseased lung is of entirely salutary nature. The progress of the tuberculous foci which are thus compressed may be definitely arrested, and even areas of consolidation and cavity formation are often beneficially affected. We count among our outstanding successes many patients whose untreated lung was definitely and often actively affected prior to the induction of pneumothorax on the opposite, more diseased lung.

When, on the other hand, the intrapleural pressure is rapidly increased in such cases and the mediastinum is markedly displaced toward the untreated, less affected lung, forcibly compressing it, the threshold of safety is soon passed and deleterious effects are not long in appearing. The crowding of the untreated organ and the great amount of atelectasis produced in it may endanger life by the marked diminution in the respiratory function of the only working lung. Furthermore, the great decrease in negativity in the intrapleural pressure on the untreated side must be overcome by more strenuous inspiratory efforts. These factors, added to the existing disability of the already overworked organ, sooner rather than later fan the

flame of activity, which, if not quickly recognized and promptly relieved, soon passes beyond our control.

Among the few therapeutic indications for a slight positive pressure, even in the presence of a flexible mediastinum, may be mentioned the existence of thick walled active vomicae and hemoptysis. However, in compressing for hemoptysis, contrary to general belief, it is not always necessary to create high intrapleural pressure. It is an accepted fact that most hemorrhages arise from branches of the pulmonary veins, which, as a rule, are easily compressible. When the bleeding is due to an erosion of an aneurysm of Rasmussen traversing a rigid walled cavity, no amount of pressure applied through a medium of pneumothorax may suffice to ligate it. There are exceptions to this rule, and in such cases, after trying a zero pressure, it may be necessary in view of the emergency to resort to higher pressures.

It is not generally appreciated that the circulatory apparatus is profoundly and unfavorably affected in cases in which the mediastinal structures are markedly dislocated. As it has been shown, a diminution in the negativity of the intrapleural pressure at once interferes with, if it does not completely destroy, the aspiratory factor in the venous blood return, which can be compensated for only by increased cardiac action. The dyspnea and cyanosis attending marked mediastinal displacements are in a great measure due to cardiac embarrassment and perhaps kinking of some of the larger vessels.

Experience has taught that although the heart will tolerate a great deal of dislocation and accommodate itself to its new position and altered intrathoracic pressure, if these take place gradually, it will nevertheless be severely embarrassed if this new position and pressure relation are quickly changed. It is for this reason that severe cardiorespiratory failure and even death may occur as a result of sudden and marked disturbance of intrapleural tension following aspiration of copious pleural effusions. The rapid restoration of the intrathoracic equilibrium to which the heart had recently accommodated itself by the inflation of gas into the affected pleural cavity will in a few seconds relieve this distressing chain of symptoms, and may even prevent a fatal issue.

## SUMMARY AND CONCLUSIONS

The study of the pneumodynamics in general and its mechanism in pneumothorax, and the experimental evidence on the effect of pneumothorax on the intrathoracic equilibrium, as well as the accumulated clinical experience, helped us to formulate certain guiding principles in the management of pneumothorax cases as far as pressures are concerned.

In initial inflations and in the early refills, it is imperative to alter the intrathoracic conditions as gradually as possible. (It is our usual procedure to give the patient from 200 to 400 c.c. at each of the first few refills, gradually lengthening the intervals from one to seven days, and cautiously raising the amount of gas and pressure.) This allows the patient to pass through this period of compression with as little discomfort as possible. From the study of the signs and symptoms during this period, as well as from the roentgenoscopic appearance of the treated and untreated lungs, it is possible to determine the optimal pressure for each case.

In the presence of a flexible mediastinum, high pressure should at all times be avoided. A slight positive pressure may be given only in the presence of strong indications (hemorrhage, thick walled active vomicae). This principle is particularly adhered to when there is considerable involvement of the untreated side. Here again each case must be individualized and carefully observed.

Sudden changes in the intrathoracic conditions should never be permitted. For this reason all connections with the pneumothorax apparatus should be prearranged in aspirating hydropneumothorax cases, to enable us to reinflate quickly if necessary. Failure to do this may give rise to distressing symptoms and even lead to a fatal issue as a result of acute cardio-respiratory embarrassment.

In brief, our guiding principles in the management of pressures in pneumothorax are:

1. To avoid sudden change in the intrathoracic equilibrium and in the relative position of the intrathoracic viscera.

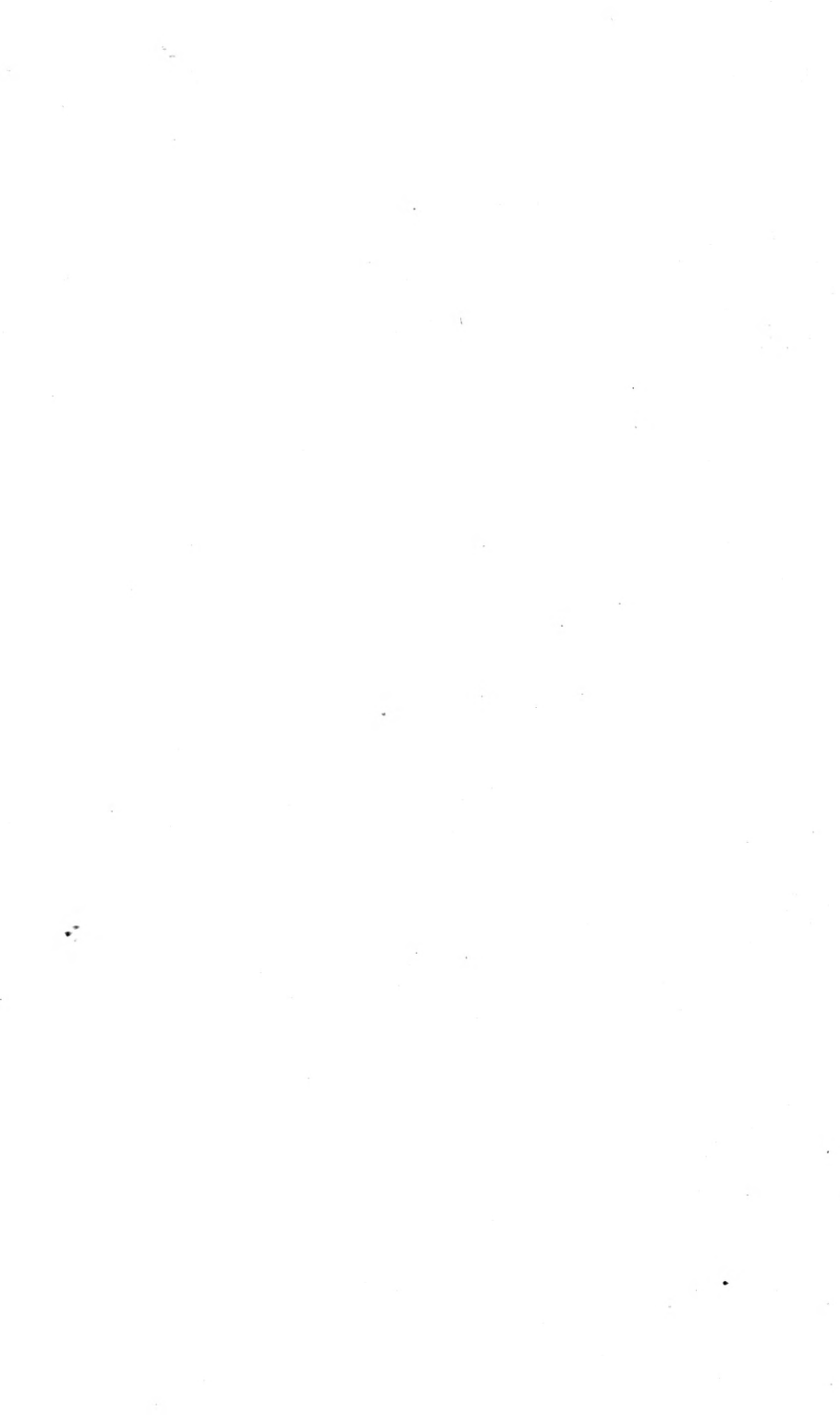
2. To avoid high pressures in the presence of a flexible mediastinum.

3. Gradually but definitely to increase the positive intrapleural pressure in cases in which pleural obliteration is threatening.

4. To individualize the cases, determining the optimal pressure requirement of each.

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# Discernment of Intrathoracic Neoplasms by Aid of Diagnostic Pneumothorax

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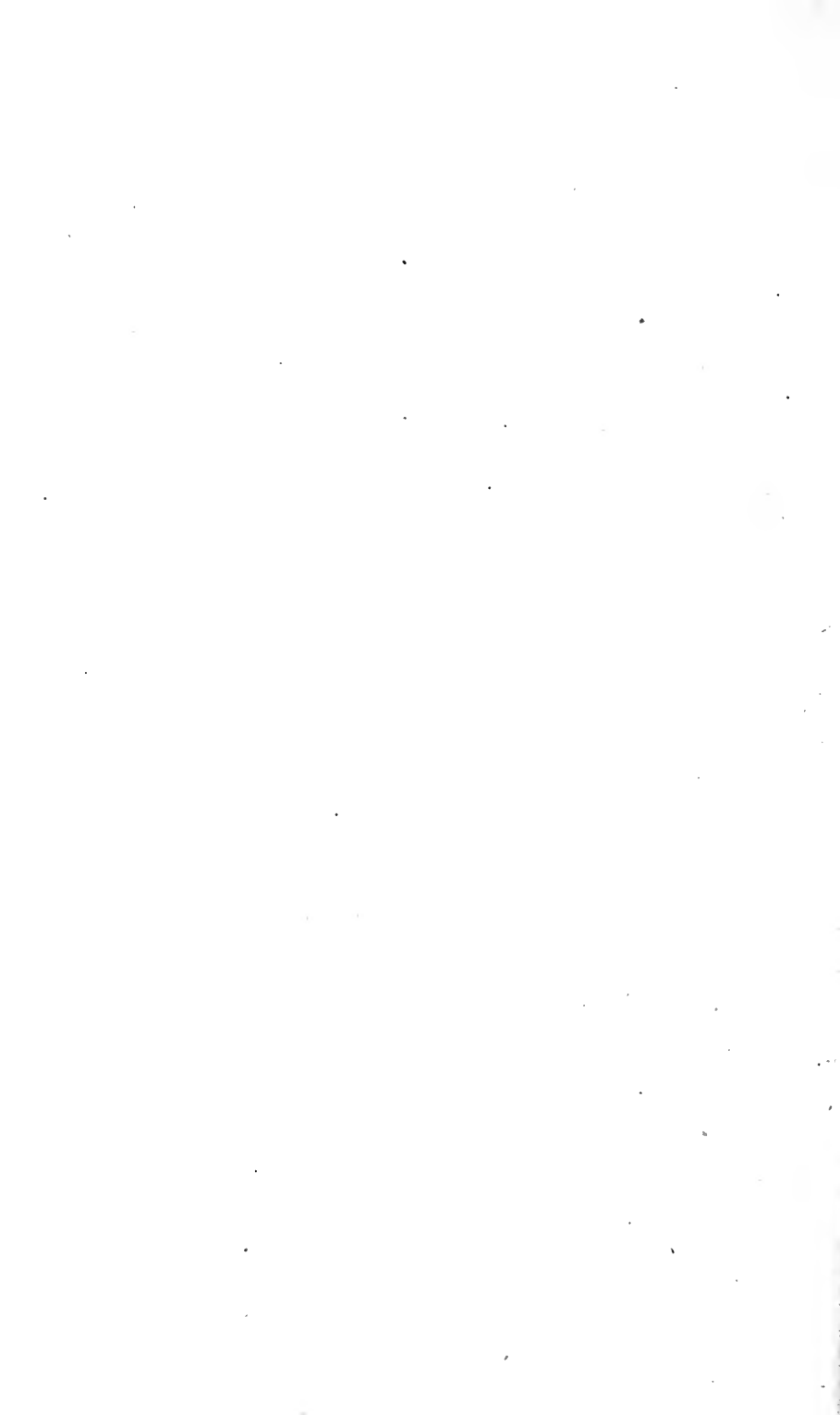
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**Discernment of Intrathoracic Neo-  
plasms by Aid of Diagnostic  
Pneumothorax**

MAURICE FISHBERG, M.D.

NEW YORK



## DISCERNMENT OF INTRATHORACIC NEOPLASMS BY AID OF DIAG- NOSTIC PNEUMOTHORAX

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NEW YORK

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The diagnosis of intrathoracic neoplasms has been considered very difficult; most of the cases are recognized only at necropsy. The reasons are clear: During the early stages, when the tumor is small, it produces only slight symptoms, and the signs elicited on physical exploration of the chest are very indefinite. The similarity of the symptoms and signs with those of early pulmonary tuberculosis is responsible for the fact that most of these patients are treated for tuberculosis, often till the end. In about 50 per cent. of cases pleural effusions (serous, sanguineous or purulent) take place and the diagnosis is then rendered even more difficult. Others expectorate fetid sputum, have fever, and a diagnosis of abscess of the lung, pleural vomica, etc. is made.

Roentgenography is in many cases of immense assistance, but in others it is of slight value and, like the history, symptomatology and physical signs, can prove merely suggestive. When the tumor is small either it is altogether invisible on the plate, or when it does cast a shadow, this is often not unlike that cast by a tuberculous lesion of the lung. In many cases the differentiation of these shadows is extremely difficult. When an effusion takes place, the entire half of the affected side of the chest is obscured by a dense homogeneous shadow, and the roentgenographer reports merely "pleural effusion." Many of this type of cases have come under my attention.

While tapping a pleural effusion secondary to carcinoma of the lung, an intern at the Montefiore Hospital accidentally injured the visceral pleura and thus a pneumothorax resulted. A roentgenogram taken of this chest showed clearly a hydropneumothorax of the right side, and a tumor adjoining the mediastinum

(Figs. 1 and 2). This accidental observation gave me the idea to utilize diagnostic pneumothorax for the purpose of discernment of intrathoracic neoplasms along the lines of pneumoperitoneum, used in intra-abdominal conditions. Carefully searching the literature, however, I found that this method had already been suggested by Brauer,<sup>1</sup> and attempted by Schroeder.<sup>2</sup> But it appears from the roentgenograms published by Schroeder that his success with this method was rather limited. It thus appears that the accom-

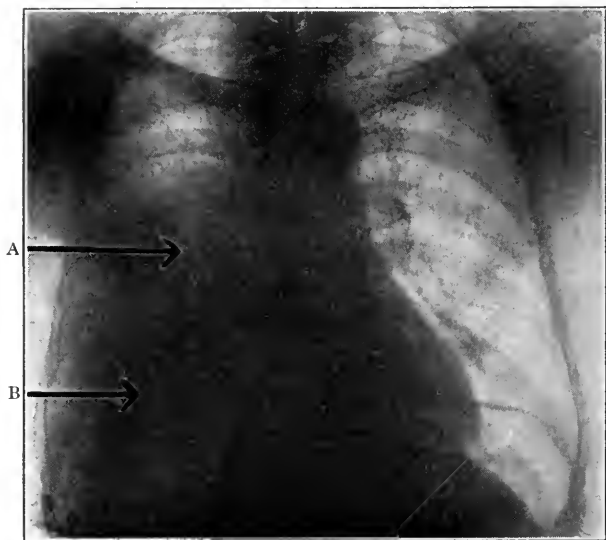


Fig. 1.—Neoplasm in right side of the chest with pleural effusion: A, tumor; B, effusion, which obscures the neoplasm.

panying roentgenograms of diagnostic pneumothorax for intrathoracic neoplasms are the first that show the tumors clearly.

In cases in which there is no pleural effusions, the technic is simple. We employ the usual technic of artificial pneumothorax, injecting several hundred cubic centimeters of nitrogen or air into the pleural cavity, using any of the standard apparatus and a

1. Brauer, L.: Aerzt. Verein zu Hamburg, Session of May 7, 1912, München. med. Wchnschr. **59**:1192, 1912.

2. Schroeder, G.: Internat. Centralbl. f. d. ges. Tuberk. Forsch. **10**: 354, 1916.

manometer for the purpose. When the lung is collapsed, the solid tumor is clearly seen on the plate. In those in whom an effusion has occurred and it is suspected that it is secondary to a neoplasm, the fluid is first withdrawn with a Potain apparatus. The pneumothorax apparatus may then be connected with the needle which is already in the chest, and the air allowed to flow in. In cases in which the fluid is purulent, and this is not at all rare in neoplasms of the lung and pleura, the needle used for tapping is withdrawn and an ordinary pneumothorax needle is inserted. The

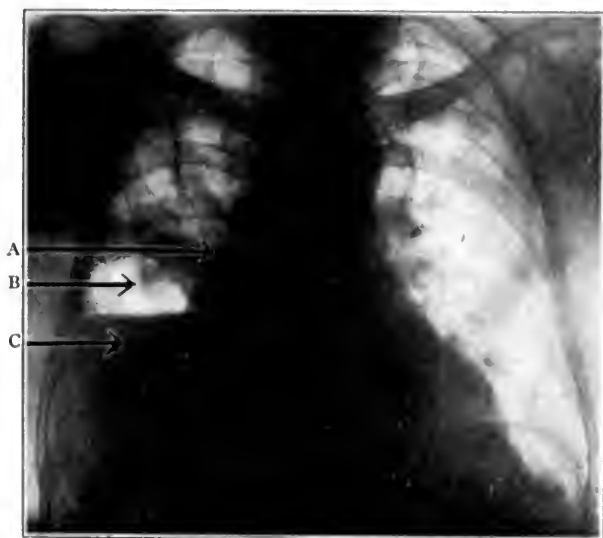


Fig. 2.—Same chest after a pneumothorax was induced: *A*, the tumor clearly differentiated; *B*, air in the pleural cavity; *C*, effusion.

amount of gas allowed to flow into the pleura varies in accordance with the condition of the patient and the pressure read on the manometer. If the patient is comfortable, as much as 1,000 c.c. of air may be allowed to enter the pleural cavity. If he suffers from severe pain or dyspnea, less is injected. In our clinic we always stopped when the positive pressure registered in the manometer reached 10 c.c. of water.

Immediately after the pneumothorax has been induced, the patient is examined fluoroscopically, and one or two roentgenograms are made. It is impor-

tant that the plates should be taken with the patient in the erect posture; otherwise the fluid within the chest, which is shifting, will spread out all over the pleural cavity and mar the picture.

#### REPORT OF CASES

Some of the cases in which roentgenograms were taken at the Montefiore Hospital will prove of interest:

CASE 1.—B. K., a man, aged 56, had primary carcinoma of the right lung which invaded the anterior portions of the

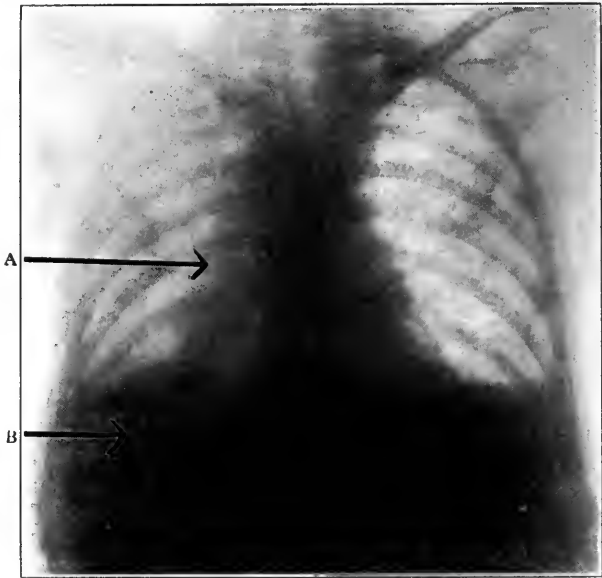


Fig. 3 (Case 3).—Large carcinoma in right lung; carcinomatosis all over left lung; effusion obscuring the tumor; picture almost typical of miliary tuberculosis with pleural effusion in right side: *A*, tumor; *B*, effusion.

second and third ribs anteriorly. The right chest was filled with fluid in which large cells resembling alveolar epithelial cells, and also many polymorphous lymphocytes were found microscopically. No micro-organisms could be found in the fluid. Sept. 9, 1920, some pale, straw-colored fluid was withdrawn from the chest with a Potain apparatus, and 500 c.c. of air injected immediately. In the roentgenogram the air within the pleura was plainly visible in the lower half of the right chest near the axilla, while the tumor, which filled more than four fifths of the right half of the thorax, produced a



dense, homogeneous shadow. It could not now be mistaken for fluid, and the pleurisy in this case was thus shown to be secondary to an intrathoracic neoplasm.

CASE 2.—B. E., a man, aged 50, had primary papilloma of the left lung, subsequently verified by necropsy. There was no fluid in the chest. With a pneumothorax apparatus, 600 c.c. of air was injected into the pleural cavity and a roentgenogram taken immediately. This disclosed the pneumothorax in the left chest very clearly, while the tumor adjoining the mediastinum was clear-cut and unmistakable.

CASE 3.—E. P., a woman, aged 42, had primary carcinoma of the right lung, subsequently verified by necropsy. As will

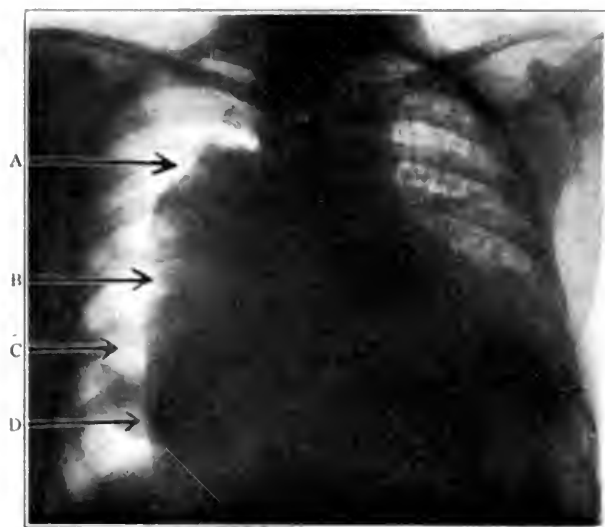


Fig. 4 (Case 3). Appearance after fluid had been withdrawn and air substituted: A, D, tumor masses; C, pneumothorax; B, collapsed lung.

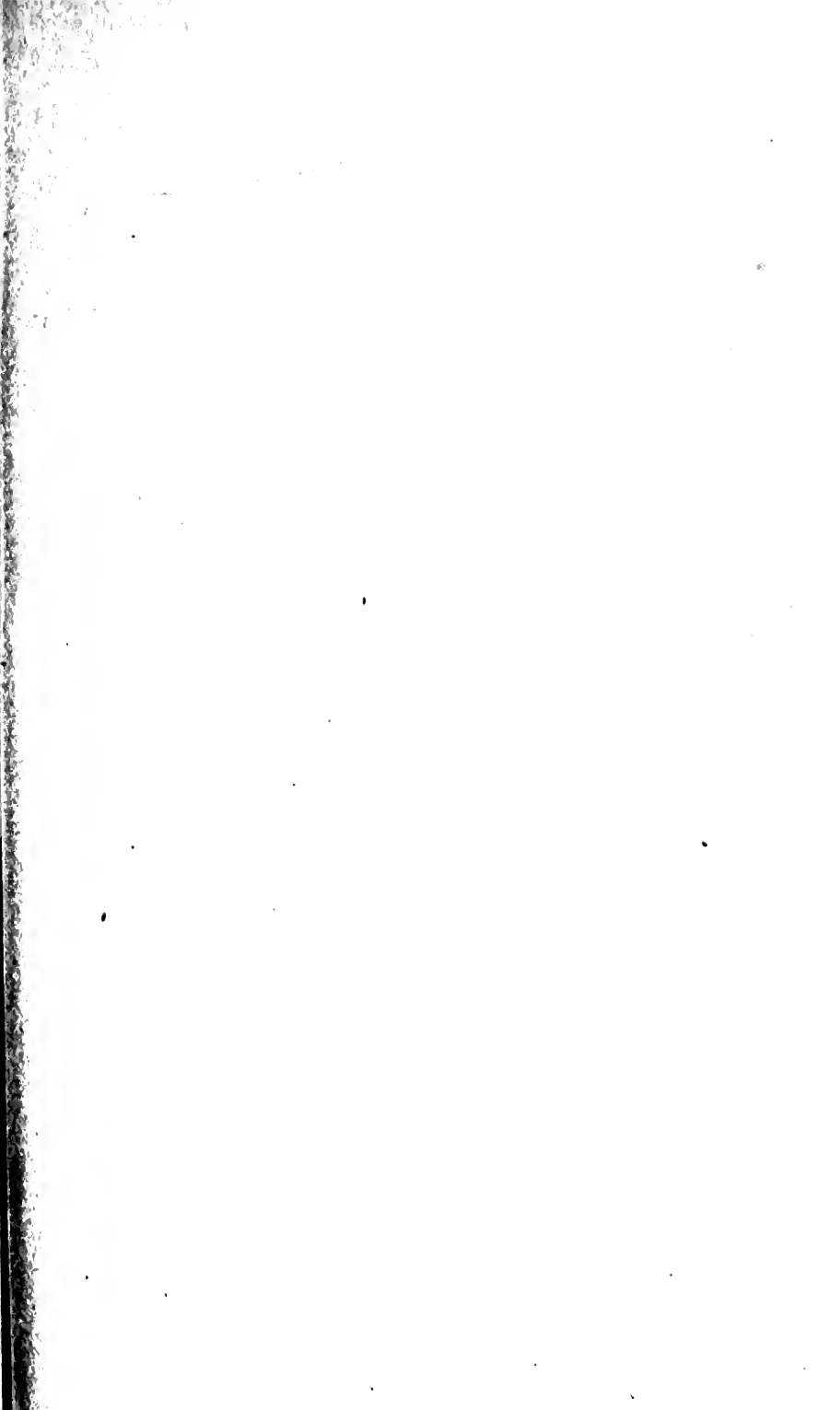
be seen from Figure 3, roentgenography could detect with certainty only an effusion into the right pleural cavity. The mottlings all over both lungs fields were not unlike those produced by miliary tuberculous lesions. In fact, several experienced in reading plates have diagnosed miliary tuberculosis of both lungs with an effusion into the left pleura. Nov. 16, 1920, 500 c.c. of slightly turbid fluid was withdrawn from the right pleura; November 18, another 300 c.c. of fluid was withdrawn. Microscopically, lymphocytes and endothelial cells were found. A section of the sediment of the fluid also revealed tumor cells. The details of these cases will be reported later on.

Immediately after the second tapping, the needle used for withdrawing the fluid was connected with a pneumothorax apparatus and 650 c.c. of air was allowed to flow into the pleural cavity, till a positive pressure of 10 c.c. of water was registered on the manometer. The roentgenogram (Fig. 4) taken immediately after the pneumothorax was induced shows the right pleural cavity filled with air, the lung collapsed near the mediastinum; and two tumor masses, one extending from the second to the third interspace, and the other from the fourth to the sixth interspace can be made out very clearly. Necropsy performed December 25, confirmed these findings. The mottling all over both lung areas is thus shown not to be miliary tuberculosis, as would be thought at first sight, but miliary carcinomatosis.

#### COMMENT

In view of the harmlessness of the procedure, it appears that it should be utilized for diagnostic purposes in all doubtful cases. While most tumors can be diagnosed merely by a careful study of the history and physical signs of the cases, as will be shown in a later communication, this procedure of diagnostic pneumothorax will in many cases, especially those with pleural effusions, clear up the diagnosis promptly and decisively. It is doubtful whether it is advisable to induce a pneumothorax in cases with aneurysm.

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## LYMPHATISM AND TUBERCULOSIS

BY MAURICE FISHERG, M.D.

NEW YORK

MEDICAL literature of the past twenty-five years abounds in statements to the effect that hyperplasia of the lymphoid tissue of the rhino-pharynx is one of the most potent predisposing factors in the evolution of tuberculous disease of the lungs. Many physicians insist that surgical treatment, in most cases implying complete removal of the lymphoid tissue in the throat, will prevent tuberculosis, and favor recovery from existing disease. For this reason operations on the nose and throat have been extremely frequent in those who suffer from pulmonary tuberculosis, as well as in those who are said to be predisposed to the disease.

Following these teachings, I have often referred tuberculous patients to competent specialists for the removal of the lymphoid tissue in Waldeyer's tonsillar ring. But during recent years my attention has been drawn to another phase of this problem. A large number of patients have stated that their lung symptoms made their appearance soon after operations of the sort just mentioned. That it could not justly be attributed to coincidence was apparently confirmed by another fact. Too many tuberculous patients who had been doing quite well, began to show manifestations of increased activity in the constitutional symptoms and extension of the lung lesions soon after operations for the removal of tonsils and adenoids were performed.

These clinical facts have led to further investigations on lymphatism and pulmonary tuberculosis, and it appears that there exists a certain etiological and prognostic relationship between the amount of lymphoid tissue in the throat and the development of tuberculous disease of the lung.

Hypertrophied lymphoid tissue in Waldeyer's tonsillar ring is a manifestation of the lymphatic diathesis, or *status lymphaticus*. Individuals with the lymphatic constitution are recognized clinically when the stigmata of the dyscrasia are well marked on the exterior of the body; when the bodily configuration and the distribution of the hair are heterosexual, the skin in the male delicate, the eye lashes long, etc. Some of the stigmata of this dyscrasia, such as hypoplasia of the heart and aorta, hyperplasia of the lymphoid follicles of the spleen, intestines, etc., can only be recognized with certainty at the necropsy. When the thymus is also more or less enlarged, and remains so at maturity, which is not infrequent in lymphatics, we speak of the *status thymico-lymphaticus*. These, however, are extreme instances of this constitution which are comparatively

uncommon. As in other congenital anomalies consistent with existence, there are various degrees of the lymphatic constitution. In some it affects many organs, the lymphoid tissues of the rhino-pharynx, the thymus, the spleen, the intestines, etc., while in others the tonsillar ring alone, the faucial and especially the lingual and pharyngeal tonsils, as well as the lymphoid follicles of the posterior wall and lateral folds of the pharynx, are hyperplastic. It is with the relation of these structures to the evolution of active pulmonary tuberculosis that we are concerned in this communication. In fact, it is the opinion of those who have studied the problem of lymphatism, like Paltauf,<sup>1</sup> Bauer,<sup>2</sup> Neusser,<sup>3</sup> Mosse,<sup>4</sup> and many others, that while this dyscrasia cannot always be diagnosed clinically with certainty, the hyperplastic condition of the lymphoid tissue in the tonsillar ring, especially when the lingual and pharyngeal follicles are found enlarged, is an indication of some degree of lymphatism.

However, one thing must be borne in mind in this connection. The faucial tonsils are very often found enlarged as a result of inflammatory processes in individuals who show no signs of anything like the lymphatic constitution. But in these cases, as a rule, it is only the faucial tonsil that is hyperplastic, and in many cases the enlargement is the result of frequently repeated acute and subacute inflammatory processes of the tonsils. In lymphatics the lingual and pharyngeal tonsils are enlarged and usually congested. This point should never be lost sight of when evaluating the relation of lymphatism to tuberculosis.

Lymphatics are very prone to acute infectious diseases, and when affected, succumb in larger numbers than others in whom the lymphoid tissue in the throat is not hyperplastic. This is the case with cerebro-spinal meningitis, diphtheria, scarlet fever, etc. Moreover, lymphatic children are very frequently scrofulous and rachitic.

On the other hand, though delicate and subject to various contagious diseases, lymphatics have been found singularly less prone to develop active and progressive tuberculous lesions in the lungs than others in whom the lymphoid tissue is normal. Autopsies reported by Bartel,<sup>5</sup> Symmers,<sup>6</sup> Emerson,<sup>7</sup> Ewing,<sup>8</sup> and many others, have shown that active tuberculous lesions of the lungs are extremely rare among lymphatics. Bartel has observed that among women who died from eclampsia, and also among suicides, an enormous proportion of whom are of the lymphatic diathesis, active tuberculous lesions of the lungs are strikingly rare when examined on the necropsy table.

Persons of the lymphatic diathesis are infected with tubercle bacilli as often as others. The fact that the tuberculin reaction is positive in them to the same extent as in others indicates that they harbor tubercle bacilli. Careful dissection at necropsies have shown that they, as a rule, have tuberculous lesions of the glands, lungs and serous membranes. But these lesions are, in the vast majority of cases, healed through cicatrization or calcification. It appears that in them the glands respond more promptly and more effectively to the infection. In many of these the infection is followed by disease. But it is the glands, bones, joints and

the serous membranes that are mainly affected, while the lungs are, as a rule, spared. When lung lesions are discovered at the necropsy in lymphatic individuals they show strong manifestations of the processes of repair.

It is important to recall in this connection that for generations clinicians have observed the extraordinary freedom from pulmonary tuberculosis of scrofulous children, and of adults who, during childhood, had been scrofulous. The rarity of scars on the neck, indicating past glandular tuberculosis, among tuberculous adults points in the same direction. Scrofula is considered a manifestation of lymphatism on which tuberculous infection has been implanted; it has been looked at as a defense reaction on the part of the glands of the body against the invasion of tubercle bacilli.

My attention to the relation of lymphatism to pulmonary tuberculosis has also been drawn recently by another clinical observation. In patients with active and progressive tuberculosis of the lungs, especially in the terminal stages of the disease, the throat is pale, and in many the sinus tonsillaris is excavated; hardly any tonsils are visible. Moreover, other lymphoid structures are almost never seen in the throats of these patients; there are no lingual tonsils, no adenoids, while lymphoid follicles on the posterior wall of the pharynx are extremely rare in tuberculous patients in the final stages of the disease.

A pulmonary lesion developing in a patient who lacks lymphoid tissue in the tonsillar ring pursues a very acutely progressive course. This clinical fact has such important prognostic bearings that it is worthy of further investigation. On the other hand, active pulmonary tuberculosis is now and then seen in patients with signs of the lymphatic diathesis; constitutional symptoms and signs of the disease may be in abundance, and tubercle bacilli may be found in the sputum. But when it is observed that the course of the disease is mild, the lesion shows marked tendencies to sclerosis. I am under the impression that these lymphatics contribute a large proportion of the favorable tuberculous cases, as well as the abortive cases of which more will be said later on. Hyperplasia of the lymphoid tissue in the throat is also at times found in patients with extensive lesions in the lungs of long duration. But here again the following peculiarities may usually be noted: In most instances the pleura is involved, at times the whole pleura is found thickened and adherent, while a large pulmonary cavity may be found in one of the upper lobes. It is, however, a striking fact that despite the extensive destruction of lung tissue, the patient is doing comparatively well, the constitutional symptoms are mild, while the lung in the opposite side of the chest remains singularly free from active tuberculous changes, which is rare in patients with extensive lesions but in whom the lymphoid tissue in the throat is normal or subnormal in amount.

In several lymphatics with tuberculous lung lesions of the type mentioned, operations for the removal of the tonsils and adenoids were performed, and the results were disastrous. The tuberculous lesions ex-

tended, the opposite lung was invaded by tubercle, while the larynx and intestines soon showed signs of infection. Many of this type of patients have recently been observed in private practice, while several are annually admitted to my hospital service in a moribund condition. They state that though tuberculous, they had been doing very well till the operation on the throat was performed.

To verify this observation I asked Dr. J. J. Wiener, one of my associates, to go over carefully all the patients in the tuberculosis pavilion of the Montefiore Hospital with a view of ascertaining the presence or absence of lymphoid tissue in the throat in relation to the activity and progressiveness of the lung lesions. He reported that those with hyperplasia of the lymphoid tissue in the throat are almost invariably doing well, or fairly well, despite evidences of extensive destruction of pulmonary parenchyma in some of the patients, while those in whom the lymphoid tissue in the throat is scanty or lacking are almost invariably going down. His observations led him to the conclusion that extremes, complete absence of tonsils on the one hand, and very much enlarged faucial and lingual tonsils on the other, bear out this rule more strongly than borderland cases. The statistical data thus collected will be published in due time.

It is noteworthy in this connection that patients with acute or chronic, but active, tuberculous lesions in the lungs only rarely suffer from the endemic and epidemic acute infections of the nose and throat. I have repeatedly observed during epidemics of coryza, grippe, tonsillitis, etc., that the vast majority of tuberculous patients escape though other members of their families are affected one after another. In sanatoria and hospitals for tuberculous patients it is a common observation during such epidemics that the personnel, the physicians, nurses, orderlies, etc., are laid up one after another, while among the patients the chances of contracting any of these acute infections of the nose and throat are in inverse ratio to the activity and progressiveness of the pulmonary process. Those having latent or mild lesions, showing but slight tendencies to extension, may suffer slightly from the epidemic "cold" or "grippe;" those with active disease only rarely contract the complicating infection, and then the "cold" is mild, hardly inconveniencing; while those with active and progressive pulmonary tuberculous lesion escape altogether, as a rule. This is observed in institutions where the chances of contracting the infection are about the same for all classes. An observant patient who had been tuberculous for many years, having gone through the usual exacerbations and remissions of the disease, told me that he believed that his lung lesion was in abeyance because he again became subject to attacks of coryza during epidemics. Somewhat similar observations were made during the epidemics of influenza of 1918-1920.

It is important to interpolate here that tuberculous patients often suffer from exposure. But in them the "cold" manifests itself in an exacerbation or extension of the lung lesion, and not as an acute inflammatory process of the nose and throat. In tuberculous patients who date back the onset of the lung disease to a "cold" it is almost invariably found



that the initial symptoms referred to the pleura, bronchi and lungs, and not to the nose and throat.

The relation of lymphatism to pulmonary tuberculosis is already noted during childhood. Between three and twelve years of age the lymphoid tissues are highly evolved and they promptly respond to nearly all infections. For this reason acute and subacute infections of the tonsils, adenoids and nasal mucous membrane are very common. And it is a striking fact that during this period of life pulmonary tuberculosis is exceedingly rare. Moreover, in the few instances that have been seen by the writer, the tonsils were small, almost lacking, the soft palate and posterior wall of the pharynx were pale, while hardly any lymphoid follicles could be discovered at the root of the tongue; adenoid vegetations are not seen in children with tuberculosis of the lungs. In some cases the sinus tonsillaris was so deeply excavated as to suggest prior radical tonsillectomy. Similar absence of tonsils to an extent as to suggest recent radical tonsillectomy is very frequently seen in adults with tuberculous disease of the lungs running an acute and stormy course. On the other hand, many children with hyperplasia of the lymphoid tissue in the throat often present symptoms and signs of tuberculosis of the intrathoracic glands, and the prognosis in these cases is very favorable. In rare instances there are signs of pulmonary involvement, but these parenchymatous lesions tend to sclerosis, and healing of the process.

The lymphoid hyperplasia characteristic of youth often recedes in quantity and activity when maturity is reached. The lymphoid tissue in the tonsillar ring atrophies more or less during adolescence. Many conservative physicians do not remove tonsils and adenoids in children indiscriminately because they anticipate that these tissues will probably atrophy after twelve years of age. It has been a very important observation of Bartel<sup>1</sup> that the atrophy of these lymphoid tissues is not in all cases accompanied by marked diminution in the size of these structures; he found that while the lymphoid cells are destroyed, they are in many cases replaced by connective tissue. Repeated inflammatory processes, which are not rare, may also convert the tonsil into a large fibroid mass with but few lymphoid cells. For these reasons, large tonsils in adults are not always lymphoid structures, as they are during childhood. But, as a rule, it is the faucial tonsil that is thus affected by fibrosis, the lingual and pharyngeal follicles are almost always glandular in structure.

It is noteworthy that tuberculosis becomes a chronic pulmonary disease just at the age when the lymphoid tissue in Waldeyer's ring recedes in quantity and in all probability in activity. Chronic pulmonary tuberculosis is a disease of human beings over fifteen years of age. Moreover, as was already intimated, persons in whom the lingual and pharyngeal tonsils remain enlarged and functionally active are only exceptionally affected with progressive tuberculosis of the lungs. When tuberculous disease of the lungs does occur, there are strong tendencies to sclerosis and healing of the process. Now and then we even see that the lung in such individuals is extensively involved, but even then the processes of

repair are apparently stronger than the destructive processes, and the disease pursues an exceedingly chronic course.

Many authors have maintained that the syndrome first described by Krönig<sup>9</sup> under the name of "collapse induration" is really an abortive form of pulmonary tuberculosis. The symptoms are those of early phthisis; physical exploration and radiography of the chest reveal signs of an airless area of lung tissue in one of the apices, most commonly the right. But the lesion never progresses beyond that stage. Krönig pointed out that this process is found almost invariably in mouth breathers who have nasal obstruction owing to adenoids, enlarged tonsils, etc.; they all have the characteristic facies of the mouth breather, enlarged and drooping lips, obliteration of the naso-labial fold, etc. In other words, it appears that "collapse induration" is essentially abortive pulmonary tuberculosis in individuals with the lymphatic constitution. In those in whom because of lymphatism the lesion in the lung is mild and tends to speedy cicatrization though tubercle bacilli are discovered in the sputum, we speak of abortive tuberculosis.

## RECAPITULATION

General observation and necropsy reports show that individuals of lymphatic diathesis are only rarely affected with active and progressive pulmonary tuberculosis. Infection with tubercle bacilli produces fibroid lesions, and clinical manifestations of the disease are mild, showing that the processes of repair are very active.

2. The diagnosis of the status lymphaticus is very difficult, often impossible during the life of the patient. But hyperplasia of the lymphoid ring in the throat, especially the lingual and pharyngeal tonsils, may be considered as the most reliable clinical sign of the lymphatic constitution.

3. Infection with tubercle bacilli only rarely affects the lungs in lymphatic individuals, though glandular and osseous lesions are quite common. In the comparatively uncommon cases of pulmonary tuberculosis seen in lymphatics, the lesions are mild and tend to sclerosis.

4. When found in a patient with pulmonary tuberculosis hyperplasia of the lingual and pharyngeal tonsils is an indication of a good prognosis. In some of these patients the pulmonary lesion is aggravated soon after the tonsils are removed by operation. Many tuberculous patients date back the onset of symptoms of active disease to tonsillectomy.

5. Further clinical evidence in this direction is the rarity of coryza, and acute inflammatory conditions of the nose and throat in patients with active and progressive pulmonary tuberculosis.

6. In children, in whom the lymphoid ring in the throat is frequently hyperplastic, pulmonary tuberculosis is very rare; in adults, in whom the lymphoid ring is frequently hypoplastic, tuberculosis of the lungs is common.

7. In patients with far advanced pulmonary tuberculosis the tonsils,

especially the lingual and pharyngeal, are almost absent in the vast majority of cases.

8. Tuberculous infection of the lungs in lymphatic individuals produces an exceedingly chronic disease, running a benign course. In many the abortive type of the disease is observed.

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# ACTION OF RADIUM AND THE X-RAYS ON THE BLOOD AND BLOOD-FORMING ORGANS

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The Cancer Division, Montefiore Hospital  
NEW YORK

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# ACTION OF RADIUM AND THE X-RAYS ON THE BLOOD AND BLOOD-FORMING ORGANS\*

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IT is difficult to estimate correctly the mechanism of the action of any agent on the blood and the blood-forming organs. The reason for it lies in the fact that the knowledge of the individual function of the various types of blood-cells and their correlation is quite incomplete. This concerns mainly the types of cells which predominate numerically in the blood, namely, the erythrocytes, the polymorphonuclear neutrophile leucocytes and the lymphocytes.

The numerical proportion of the lymphocytes and the polymorphonuclear leucocytes differs in the various animal species. Of the animals studied by the writer and his associates, the normal blood of a turtle contains less than 10 per cent of polymorphonuclear leucocytes and over 90 per cent of lymphocytes. The blood of a frog contains from 10 to 20 per cent of polymorphonuclear leucocytes, about 80 per cent of lymphocytes and from 2 to 5 per cent of eosinophiles. The blood of a guinea pig contains about 25 per cent of polymorphonuclear leucocytes and 75 per cent of lymphocytes. The rabbit's blood contains both types of white cells in about equal amounts, and the blood of a man contains about 75 per cent of polymorphonuclear leucocytes and 25 per cent of lymphocytes. There is no clear conception as to the functional or embryological reason for this numerical difference in the proportions of the two types of white cells present in the blood of the various species of animals.

Nor is there a complete unanimity as to the influence which radium and x-rays exert on these various types of blood-cells. The majority of the investigators however maintain that the erythrocytes present the types of blood-cells most resistant to radiations, while the lymphocytes are the most radio-sensitive cells of any in the

organism. The writer has indicated in his previous publications that this "selective" biological action of the rays on the leucocytes goes even beyond the apparent structural differences of the cells. The radiations, for instance, destroy the lymphocytes in lymphatic leukemia a great deal more rapidly than the identical morphological lymphocytes in conditions of inflammatory leucocytosis. As a general rule the action of radium and x-rays on the normal blood results in the diminution of the number of lymphocytes and a relative increase in the number of the polymorphonuclear leucocytes.

The influence which radium and the x-rays exert on the lymphocytes and on the lymphoid tissue generally, of which the lymphocyte is the most important component part, is of greatest significance in the whole problem of radiotherapy. By increasing the intensity of the radiations it is undoubtedly possible to increase the destructive action on the malignant tumor, but with it goes the danger of a severe injury to the blood and the blood-forming organs. This injury will not only destroy the general resistance of the organism, but will also inhibit the power of the organism to form a protective connective tissue barrier around the tumor. It was stated by the writer on numerous previous occasions that the formation of this connective tissue wall is the most important result produced by radium and x-rays on cancer tissue, and this connective tissue formation can only take place when the lymphocytes and the lymphoid tissues of the organism remain intact.

In view of all this it is of great importance to study under different conditions and on different species of animals the action of radium and the x-rays on the blood and blood-forming organs.

In a previous publication the writer

\* Read at the Sixth Annual Meeting of THE AMERICAN RADIUM SOCIETY, Boston, June 6-7, 1921.

reported upon the action of x-rays on the blood of a turtle. Chart I shows the numerical relationship between the polymorphonuclear leucocytes and the lymphocytes before and after x-raying.

CHART I  
INFLUENCE OF X-RAYS ON LYMPHOCYTES OF  
TURTLE

Smears	Leuco- cytes	Lympho- cytes
Before x-ray.....	3	97
Immediately after.....	60	40
24 hours later.....	45	55
96 hours later.....	45	55
120 hours later.....	42	58
144 hours later.....	6	94

Chart I shows the differential count of the blood before the x-ray treatment began, immediately after the treatment, and 24, 96, 120, and 144 hours later. Numerical relationship between the two types of cells changes greatly soon after radiation, then it gradually returns to the normal, so that 12 days later the blood contains the same relative number of the cells as before radiation.

The present investigation consisted in subjecting to the action of radium and x-rays normal frogs and also frogs in whom a change in the white blood cells was induced by a preliminary injection of yeast. A similar study was also undertaken on normal rabbits.

INFLUENCE OF X-RAY ON NORMAL FROGS

The experiments were conducted in the following manner. A total and differential blood count of each animal was taken before the treatment. The whole body of the frog was then treated with the x-rays for forty-five minutes using a Coolidge tube, 9 in. spark gap, 7 ma., 8 in. focal distance and no filtration. Blood counts were taken at various intervals after radiation for a period of four days. The following results were obtained: The total leucocyte count showed a very slight difference from the normal count before radiation. The differential count showed a marked change in the numerical relationship between the polymorphonuclear leucocytes and the lymphocytes,

while the number of the eosinophiles and transitionals remained practically stationary. This change was most marked twenty-four hours after radiation, and the blood usually became normal about four days after radiation. Chart II shows a type of this series of experiments.

CHART II  
INFLUENCE OF X-RAYS ON NORMAL FROGS

Smears	Lymph.	Poly.	Eosino.
Before x-ray treatment...	84	14	2
24 hours after treatment	28	70	2

INFLUENCE OF RADIUM EMANATION ON  
NORMAL FROGS

The method consisted in the introduction into the dorsal lymph-sac of a frog of a minute capillary glass tube about 4 mm. long containing from 1.0 to 0.6 millicuries of radium emanation. This method produces slow and continuous action of the rays of radium on the organism of the animal. The results obtained on the blood were quite analogous to those produced by the x-rays. The important difference, however, consisted in the fact that the change in the numerical relationship between the polymorphonuclear leucocytes and the lymphocytes was most pronounced only about three days after the insertion of the radium emanation capillary. Chart III shows a type of this series of experiments.

CHART III

Blood Smears	Lymph.	Poly.	Eosino.
Before treatment.....	88	10	1
24 hours after insertion of radium emanation capillaries.....	64	34	2
72 hours after insertion..	13	85	2

THE INFLUENCE OF RADIUM AND X-RAYS  
ON YEASTED FROGS

The experiments consisted in the injection of an emulsion of yeast into a normal frog. This injection of yeast is followed by a change in the blood of a frog similar to the one induced by the x-rays or radium. This change is most marked twenty-four

hours after the injection and continues for a few days. This series of yeasted frogs was treated by the x-rays or radium emanation in the same manner as the first and second series reported above. Now the remarkable phenomenon observed in this series consisted in the fact that neither the x-rays nor the radium produced any further noticeable change in the numerical relationship between the polymorphonuclear leucocytes and the lymphocytes, or

The change in the numerical relationship of the polymorphonuclear leucocytes and the lymphocytes was similar to those observed in the turtles and frogs. The blood-picture became normal again in about three to four days after radiation.

The radium applications in the rabbit were done in the following manner: A laparotomy was performed and from two to four radium emanation capillaries were inserted into the spleen. Blood examina-

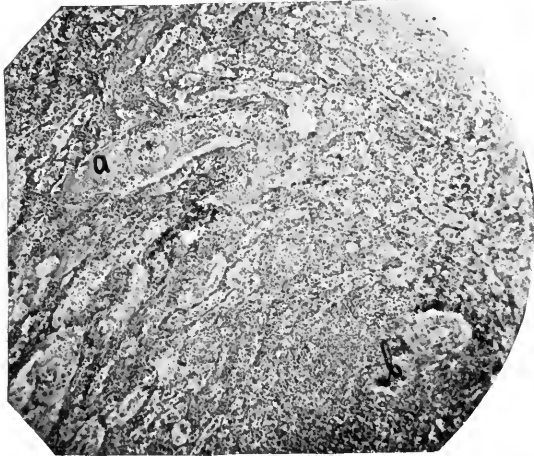


FIG. 1. Shows an area of necrosis at a and an altered blood-vessel at b.

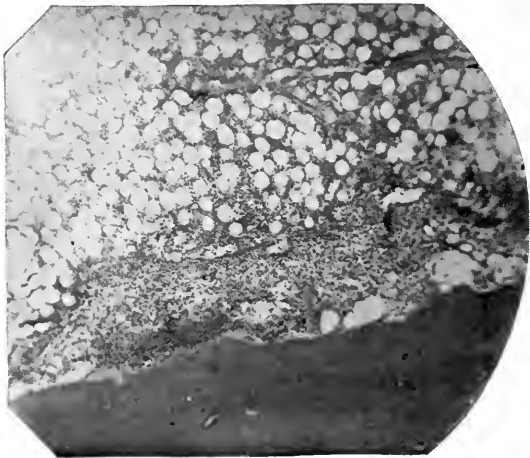


FIG. 2. Shows compact bone necrosis and alteration of bone-marrow.

at the most a very slight additional decrease of the number of lymphocytes. Chart iv presents a type of this series of experiments.

CHART IV

Blood Smears	Lymph.	Poly.	Eosino.
Before yeasting.....	76	22	2
17 hours after yeasting...	40	60	0
Immediately x-rayed and blood tested.....	29	68	3
24 hours later.....	19	80	1

THE INFLUENCE OF THE X-RAYS AND RADIUM ON NORMAL RABBITS

Normal rabbits were x-rayed with the same technique as was reported above for normal frogs. The whole body of the animal was x-rayed. The total leucocyte count again showed only a slight difference from the normal count before radiation.

tion was done before the operation and then was repeated daily for a week after the operation. In no animal was there any change noted in the blood structure. The spleen itself showed necrosis and extravasation and endarteritic changes in the walls of the blood-vessels. Figure 1 shows an area of necrosis and a cross section of an altered blood-vessel. All these changes were found in a small area surrounding the region into which capillary was placed. At a further distance from the capillary the structure of the spleen appeared to be normal. In another series of rabbits an opening was drilled into the shaft of the long bone and two or four radium emanation capillaries were placed into the bone marrow, the opening in the bone sealed with surgical wax and the skin opening sutured. All the operations on the rabbits were done under ether anesthesia. The blood of the animals was examined before the operation and daily for a week after



the operation. Again no change was noted in the blood structure. The marrow surrounding the capillary showed changes similar to those found in the spleen. Figure 2 shows an area of bone necrosis and altered bone marrow.

#### CONCLUSIONS

The results of the analysis of the experiments of this investigation tend to confirm the prevailing opinion that the lymphocyte is the most radio-sensitive cell in the animal organism. The change in the numerical relationship of the two types of white cells was not accompanied by a noticeable change in the total leucocyte count. Apparently the mechanism of the action of the rays on the leucocytes of the blood consists in the destruction of the lymphocytes, which is then followed by the release of the polymorphonuclear leucocytes from the bone marrow or by an overproduction of this type of cells by the blood-forming organs.

Certain investigators maintain that the polymorphonuclear leucocytes are the type of the blood-cells most readily destroyed by the rays. However, the analysis of their results shows that the destruction of the polymorphonuclear leucocytes only takes place as the final result of the action of a lethal dose of the rays which produces ultimately a severe general leucopenia. The following instance from a publication of Zoellner illustrates the point. The blood of a guinea pig before radiation showed 85 per cent of lymphocytes and 15 per cent of polymorphonuclear leucocytes, two days after radiation it showed 46 per cent of lymphocytes and 54 per cent of polymorphonuclear leucocytes, and three days after radiation 24 per cent of lymphocytes and 76 per cent of polymorphonuclear leucocytes. The total blood count was not changed perceptibly all this time. Since the animals received a lethal dose of radiation, there developed near death a severe leucopenia of from 12,000 to about 600 white cells, so that the whole blood smear showed one or two lymphocytes and no polymorphonuclear leucocytes.

In the present investigation, however, only such amounts of radium and x-ray

were given that the animals could completely recover after the lapse of a certain time and the blood picture again became normal. The most important phenomenon observed in the course of this study is the difference with which the two species of animals, the frog and the rabbit, react to the action of radium and the x-rays. In the frog the same general effect was obtained on the blood by the amount of x-raying employed in this investigation, as well as by the insertion of a glass capillary containing 1.0 to 9.6 millicuries of radium emanation. The blood of the rabbits reacted to the x-rays in a manner identical with that of the frog. On the other hand, an insertion into the spleen or the bone marrow of a rabbit of 2 or 4 capillaries, i.e., two or four times the amount of radium emanation inserted into the frogs, produced no change in the blood of the rabbit, though it produced marked local effect on the spleen and bone marrow. These comparative findings in the two species of animals and the two types of radiation are of considerable importance to the subject of radiotherapy from two following standpoints:

The subjects of the relative therapeutic efficiency of radium and x-rays, of the higher or lower voltage of the electric current producing the x-rays, of the correct methods of physical measurement of the rays, whether photographic or ionization methods, for instance, and the correct amounts to be used, are in the order of the day. However, these subjects are treated chiefly from the standpoint of physics rather than from that of biology. There cannot be any doubt that measured by photographic or ionization methods or generally considered from its physical aspect one x-ray application as employed in the present investigation and one capillary tube containing 1.0 or less millicurie of radium emanation inserted into the frog and left there to decay represent two qualitatively and quantitatively different entities. Nevertheless they must be considered quite analogous biologically, since they produce the identical effect on the blood of the frogs. This indicated clearly that for biology and medicine a biological standard of measurement would be of far

greater value than the physical methods. It may be added here in parenthesis that the action of the rays on normal blood and lymphoid tissue is of greater importance than their action on the skin, the more so that the radium and x-ray burns are most probably due to change in the lymphoid tissues of the walls of the blood-vessels.

The second phenomenon observed in this investigation further illustrates the importance of the biological differences for the ultimate results of the action of the rays. The x-rays produced a change in the blood-picture of the rabbit because the square surface of its body is greater than that of the frog, and consequently the former received a greater amount of radiation though all the other conditions of the x-ray apparatus were the same as those used in the frog. The radium emanation tubes produced no change in the blood of the rabbit, though the amount

was more than sufficient to produce a change in the blood of the frog. The reason for it lies in the fact that the effect is distributed in the larger quantity of the blood of the rabbit and becomes so small as not to be perceptible. At the same time the local effect of the radium emanation is very marked.

Two conclusions may thus be drawn from the analysis of the experiments. First, that radium, as compared with x-rays, will produce the same and even a more marked local effect with far less general disturbance of the blood. Second, that the larger the square surface of the entry of the x-rays into the organism the more severe is the general effect on the blood. In view of all this, biological conditions must be studied at least as much as the purely physical conditions before a true estimation of both the correct quantity and the quality of the radiations to be used in therapy will be obtained.





## EARLY SYMPTOMS OF SPINAL CANCER.

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CARCINOMA of the spine, that is, of the bodies of the vertebrae, is not a very unusual condition. Indeed the spongy bones, particularly the bodies of the vertebrae, are probably the most favored sites for the location of metastases. With increased facilities for autopsies and more thorough examination of the skeleton in patients having died of carcinoma, the pathologist has come to recognize this connection as a matter of course.

The clinician, however, not so favored, still fails to appreciate this coincidence and frequently fails to recognize metastatic carcinoma of the spine and other bones until he has had to undergo the mortification of an incorrect diagnosis and prognosis. Such failures are not, however, always due to superficial examination. It is true, of course, that those who, like orthopaedic surgeons, are insistently concerned with anomalies, infections, tuberculosis, and syphilis of the spine, are apt to bear these in mind more or less to the exclusion of much more unusual pathological processes. The mistaken diagnosis cannot, however, be wholly attributed to this cause. For though in well advanced cases with evident primary foci the diagnosis is obvious, the correct interpretation of the symptoms in the early stages is often fraught with difficulty, even with suspicions aroused and in spite of the most painstaking examination.

The difficulty is due to the fact that all pathological conditions—and this applies particularly to carcinoma—cause no definite objective symptoms as long as they remain confined within the substance of the bones. In tuberculosis and other infections it is true the focus soon leads to an inflammatory reaction on or near the surface, and this is usually manifested by muscular spasm, and as a consequence spinal rigidity. But spinal rigidity occasionally accompanies malignant disease of the spine, and there are cases in which pain and restricted motion of the spine are the only symptoms over a period of months. When a primary focus cannot be discovered, and the radiograph is negative or doubtful (not a very usual happening in such cases), the differential diagnosis will sometimes try the skill of the most expert.

Even at a later stage, when there are definite signs of bone destruction, the character of the change in the conformation of the spine is not always decisive, as is generally supposed. A well-rounded kyphosis that extends over a number of vertebræ, accompanied by rather slight and ill-defined pain, may appear in Pott's disease; on the other hand, an acute angular kyphosis is occasionally the earliest manifestation of carcinoma. We have seen cases in which it was, in the absence of a primary focus and other symptoms, very difficult, or quite impossible, to differentiate these conditions even with the aid of an expert radiographer. This, of course, is a very unusual coincidence.

Symptoms of root invasion, in the absence of the bony changes of tuberculosis or other infections, are for the most part characteristic of carcinoma. They are not, however, absolutely pathognomonic, for these symptoms sometimes present themselves as early manifestations of tumors or other diseases of the spinal meninges. The appearance of the segmental symptoms of spinal compression soon leads to the differentiation of meningeal tumor, etc., from carcinomatosis; in one case under observation the segmental symptoms of a tumor of the meninges were late in appearing and the diagnosis remained in doubt for a period of two months.

It is needless to enter into a detailed discussion of all the difficulties that may be encountered in the differentiation of spinal cancer. What has been said suffices to bring out the fact that even in the late stages, when the symptoms are usually quite definite and generally appreciated, we may occasionally be unable to make a proper diagnosis, and this in spite of the most painstaking and expert examination.

This being true, it is not surprising that cancer of the spine is often entirely unsuspected during the early stages. At this period there is little danger of mistaking the condition for mycotic or tuberculous spondylitis or other organic lesions, but there is, not a possibility, but a great probability, that the condition be misinterpreted as functional. Vague back pains, ill-defined pain on pressure over the spine or the sacro-iliac, and negative x-ray report, too readily tempt one to consider the condition functional. No doubt many of us remember such cases.

With this circumstance in mind, I decided to examine critically the rather numerous cases of carcinomatosis that have come under my notice in the Montefiore Home and elsewhere, in an attempt to discover a train of objective symptoms so characteristic that one could make the diagnosis of cancer of the spine earlier and more definitely.

Pathological processes within the vertebræ apparently cause no symptoms as long as they remain within the interior of the bone.

Symptoms appear,—(a) when the process begins to emerge from within and invade the extramedullary tissues, or, (b) when the bodies of the vertebrae have been undermined, and give way, and the spine undergoes changes in contour.

The methods of differentiating cancer from other lesions of the spine must therefore be founded upon,—(a) a characteristic manner of invading the surrounding tissues, *i. e.*, the spinal cord or roots and, (b) characteristic changes in the contour of the spine.

The symptoms of actual invasion of the spine or the spinal roots are of course striking; the continuous indescribable agony that attends the carcinomatosis of the spine is fortunately characteristic of no other pathological process. Before extensive root irritation has occurred the symptoms and objective findings are not so definite and, in the absence of a demonstrable primary focus, are often difficult to interpret. According to the leading authorities, marked continuous neuralgic pains, especially bilateral or segmental in character, not influenced by the usual therapeutic remedies, should lead one to suspect cancer. In connection with other signs and symptoms, however, they are often of service in making the diagnosis; thus, continuous bilateral sciatica often leads to the search for and the discovery of a heretofore unsuspected primary cancer. It should lead to a search for cancer in situations where primary carcinoma is sometimes overlooked, unsuspected or difficult to demonstrate; *viz.*, the lungs, thyroid, and prostate. When, however, the cancer cannot be demonstrated elsewhere, then the root symptoms, as the following case history illustrates, are difficult to interpret.

A. B. Aged 52. Previous history: For the past six months has been complaining of pain in the hypogastrium, which has gradually increased in severity until now it is difficult to relieve, and then only temporarily by morphine. He was in the care of a gastroenterologist for some months and was treated for gastric or duodenal ulcer. As he was not relieved he sought advice from a number of others and the removal of the appendix was advocated. Examination shows a fairly well nourished individual; complains of pain in the pit of the stomach, which is continuous, and not relieved by heat or change of position, and only partially by opiates. Abdomen flaccid with no signs of abnormality of the contained organs. Suggestion prompts him to describe the pain as radiating from the spine forward. Medical, physical, Wassermann, etc., negative. Spine rigid but without local tenderness; x-ray shows no definite abnormality in the spine, other bones not taken. The rigidity of the spine and the pain radiating to the hypogastrium suggested a spondylitis, and cancer was not suspected. For this reason the spine was immobilized in a plaster of Paris jacket. Instead of the

expected relief, the pain increased to such an extent that after a few days the jacket was removed. Subsequently he suffered spontaneous fracture of the ribs and developed the symptom complex of general carcinomatosis.

This case, which resembles a number of others which have come under observation, is instructive in a number of ways. It illustrates not only the difficulties in the way of diagnosis, but it suggests some differentiating factors; thus for us, continuous pain more or less segmental in character, indefinite or negative x-ray findings with spinal rigidity, particularly when the condition is exaggerated by immobilization, always leads to a search for a primary carcinoma and, even when this is absent, strongly suggests malignant disease. We have not been able to discover why immobilization increases the pain in these cases (it is likely that it prevents the patient from assuming an attitude that somewhat alleviates the suffering), but in a number of cases this aggravation of the symptoms has occurred and we now consider this coincidence as definitely suggestive of carcinomatosis.

We have concluded, from an examination of the cases, that the early signs of root involvement from carcinoma have the following clinical manifestations. The symptoms are those of sensory root irritation as distinguished from a peripheral nerve lesion. What is usually designated as a bilateral sciatica is not a sciatica, but the pain and its distribution will, on careful examination, be found to correspond to one or more roots of the sacral plexus. When the spine higher up is involved, the symptoms are clearly segmental in character; usually other sensations are intact and the motor sphere is only involved late in the disease. The pain is always greatly exaggerated by immobilization; is more or less continuous; it prevents but does not interrupt sleep as does the pain in spondylitis. These symptoms appear with or without spinal rigidity and are not infrequently present when the radiograph of the spine is negative. They are in themselves not characteristic but should always arouse suspicion and encourage the search for primary carcinoma, and, in conjunction with other suspicious signs, often secure the diagnosis.

In many of the individuals seen early, that is, before the disease has reached the extension of the vertebræ, the subjective symptoms are vague. The patient complains of pain in the back, over the sacrum or the sacroiliac joint, and frequently is unable definitely to localize it. In such cases we have tried to discover the earliest changes in the spine. That is, we have searched for the objective changes that precede the characteristic x-ray findings and the actual gross deformation of the spine of extensive cancer invasion.

Until recently our histories show that we had not demonstrated these changes. This was due to the fact that we made no careful search for



them or, as it is true of the root symptoms in many of our earlier cases, we did not properly interpret or lay sufficient stress upon them. Since we have studied the subject more intensively we have found that it is often possible to foretell the ultimate vertebra breakdown long before it actually occurs and not so rarely before the radiograph gives positive results.

Of these changes, most typical is slight dislocation forward, so that there appears a more or less definite recession of particularly one or a few spinous processes as they are successively palpated from above downward. In some of the more marked cases the palpating finger suddenly meets with a sharp depression as it reaches the subluxated vertebra.

In another group of cases we have been able to discover the presence of slight later displacements which only months afterward became pronounced. This change is due to carcinomatous invasion of the lateral processes and the ligaments of the lateral joints of the spine. In two cases we have found slight lateral displacement the only symptom except vague back pains. In the absence of demonstrable primary carcinoma, the diagnosis in these cases remained in doubt for some months, and was not definitely confirmed until symptoms of general carcinomatosis appeared. In two others, marked lateral dislocation and other changes soon followed the discovery of the slight displacement.

In another group of cases we have been able to demonstrate the compression of the bodies of individual vertebræ as it occurs very early in the disease and before it is apparent in the radiograph, by what we think is a change in the relation between the adjacent spinous processes of the affected vertebræ. Rarely, the only change is a shortening of the distance between the adjacent spinous processes; more often the change in the height of the vertebræ is complicated by a variable amount of torsion.

These changes in the contour are, of course, not absolute criteria in the absence of other symptoms. They are, however, very suggestive in connection with other symptoms not in themselves definite. In practically all the cases that we have been able to follow up, the diagnosis was substantiated. And though we are far from assuming that these slight objective differences in the contour of the spine are pathognomonic of cancer, we feel that slight lateral displacements, discrepancies in the relation between adjoining spinous processes, with or without lateral deviation or torsion, are very significant symptoms. At least they should lead one to suspect cancer, and therefore strongly stimulate the most thorough search for other evidence of carcinomatosis.

With the facilities for thorough search for primary cancer and the expert radiography at our command in all general hospitals, why, it may be asked, is it necessary to seek new clinical data, or magnify the significance of the changes we have here described? But it has been our experience that if we except the more common carcinomata the primary focus is not always easy to demonstrate. Indeed, in some of our cases the primary carcinoma in the prostate, thyroid or lungs had not been demonstrated in patients with general carcinomatosis until they came to autopsy. Nor does the radiograph always clear up the diagnosis in the early stages. We have seen cases in which the radiograph was apparently negative three or four weeks before the characteristic deformation and symptoms of advanced carcinomatosis supervened. Of course the advanced cases show characteristic changes with which all are familiar. The early pictures are, however, often negative, or cannot be definitely interpreted without additional clinical data. We have carefully re-examined a great number of the plates taken at the Montefiore Hospital, where there is a large cancer service, without being able to find definite and characteristic findings for the earliest stages. Slight changes in the outline of bodies, sometimes shown only in the oblique pictures, are the usual first signs. The only additional assistance we have derived from this source was obtained by radiographs of the other bones when the plates of the spine were negative, because we can, for technical reasons, demonstrate more easily the lesion in the femur, humerus or skull. In this we have been able to confirm the observations of others that at times cancer of the femora or other bones could be demonstrated when the symptoms apparently originated in the spine, but the plates of this region were negative. The characteristic small, well-defined shadows due to multilocular growths are striking, but occur late, and the early x-ray diagnosis must usually rest on a careful study of all ill-defined shadows so often described as "picture unsatisfactory." These lesions are rapid in growth and the comparison of weekly radiographs will show an increase of a suspected lesion and allow us to state that real atrophy exists, not comparative atrophy.

On the whole, then, according to my investigation, the early diagnosis of cancer must be in many cases tentative. It can be verified by the search and demonstration of primary foci elsewhere. In conjunction with other symptoms, in themselves not decisive, the peculiar character of the root or segmental symptoms, or the early changes in the conformation of the spine here described, will often greatly aid in securing the diagnosis.

I herewith append an abstract and an analysis of the history of thirty-two cases of cancer of the spine under observation at the Monte-

flore Hospital on whom satisfactory data were obtainable. I am indebted to Dr. I. Levine who has charge of the Cancer Service for permitting me to use his cases.

The site of the primary lesion was found to be in the breast eighteen times, lung four, prostate five, thyroid three, kidney one, pancreas one, in a total of thirty-two carcinomata. The metastatic symptoms appeared before the primary focus could be determined in twelve cases. Three cases in addition, presenting spinal symptoms, had breast operations eight years previous without recurrence, and the symptoms of the metastases took that length of time to become evident. The primary lesion was not found at all clinically in six cases and proved at autopsy to be in the breast one, thyroid two, lung one, prostate two. Pathological fractures were present before the diagnosis of carcinoma was established in the spine four times, femur three, humerus two, elsewhere two. The first symptoms in seven cases, in which there had been no local pains, were fractures following slight trauma. Local spinal symptoms were present in twenty cases early in the history; ten showed pain on local pressure, and fourteen deformity. In no case was there tumor present on the spine, and sacral tumors in three cases appeared only late in the disease. Spinal pains were complained of in nineteen cases and were an early symptom in nine cases. In fifteen cases the lower extremities were the seat of pain and in thirteen cases this was an early symptom. Symptoms of metastases, other than spinal, were present in sixteen cases and early in thirteen cases. Sensation of cold was complained of in thirteen cases, and herpes zoster was found in two cases. We found positive spinal x-rays in fifteen cases and in eight they were negative. Of the eight negative cases, three showed lesions in other bones. The cases with early cord and root symptoms, as a rule, gave negative pictures at the time of onset and some even at the end. Our cases presenting metastatic bone and cord symptoms gave an average duration of fourteen months. The duration of nerve symptoms in seventeen cases averaged ten months, and fifteen cases had no symptoms referable to the central nervous system.

CASE 1.—01207. E. H., female, aged 60 years. Admitted April 9, 1917; died April 13, 1917. October, 1915, had pain in right foot and knee grew gradually worse and was bedridden all winter. April, 1916, was seven weeks at C. N. Hospital for constant pain in lower portion of spine and weakness of both lower limbs. X-ray diagnosis—Pott's disease. Six weeks in plaster corset; after removal of corset developed hematuria. October, 1916, was sent to Mount Sinai Hospital where hematuria was controlled and examination showed round diffuse kyphos in upper dorsal region with immobility but no acute spasm.

Vertebræ not sensitive. Paralysis of lower extremities. X-ray showed almost complete destruction of second and third lumbar and changes in the 1st, 4th, and 5th lumbar vertebræ. Diagnosis, T. B. C. or malignant. On admission to Home—for last six months increased frequency of urination—for one month complete transverse myelitis. X-ray—large neoplasm entire lumbar spine, metastases in dorsal spine, femora, ribs, signs of arthritis deformans. Autopsy—Carcinoma breast, metastases in spine 7 to 11 D, 2 to 5 L, skull, bones, liver, glands.

CASE 2.—PP 14. H. McM., age 79 years. Admitted, May 30, 1917; died September 11, 1917. For several months indefinite pains in back, sticking in character and fairly constant, not influenced by treatment or medication. X-rays,—kidneys negative, spine moderate arthritic changes. Spinal brace for arthritis made pains worse. Unable to wear brace. On admission severe pains in back and shoulders, pains in legs, and weakness. X-ray in July, 1917, showed aneurysm in arch of the aorta, heart enlarged, lungs negative, no bone changes. The paralysis of legs gradually increased, followed by a transient Brown-Séquard crossed paralysis, and on September 5th complete paraplegia below the waist and a gradual kyphos at dorso-lumbar region. Prostate enlarged with hard nodules. Diagnosis: carcinoma of prostate, metastases of spine and cord.

CASE 3.—02150. H. H., male, age 48 years. Admitted, March 12, 1919; died April 12, 1919. September 10, 1918, on jumping from a street car had severe pain in heel and toes of right foot. A week later was told he had a fracture. Massage and baking ordered but discontinued on account of excessive pain. In plaster of Paris for five weeks. Removal of plaster aggravated the pain. Then pills and five intravenous because blood was positive. January 20, 1919, amputation of leg was made; since that time noticed swelling at groin and at finger. On admission, has a sacro-iliac tumor, apparently osseous. March 23d, cerebral thrombosis, facial palsy followed by partial recovery. Autopsy—primary carcinoma lungs, metastases of bones, sacrum, skull, hands, liver, adrenal, lymph glands, dura, scoliosis.

CASE 4.—0943. Male, age 62. Admitted, April 11, 1916; died, September 7, 1916. For seven months had chills, weakness, dyspnoea, loss of weight. On admission:—expectoration, pain in chest, lung signs. July 21, 1916, painful nodule on clavicle, later pathological fracture. X-ray:—April 24, 1916—cavities and fluid in lungs. July 25, 1916,—pathological fracture of clavicle. Autopsy:—carcinoma of lung with extension of mediastinum, involving 4th and 5th dorsal vertebræ. Collapse of bodies and extension into outer layer of dura.

CASE 5.—0841. Male, age 52 years. Admitted, December 16, 1915; died May 6, 1916. Two years ago had cutting pain in left lower extremity from pelvis radiating down the inner side to ankle, and six months later similar pains in right limb. Plaster jacket for six months

did not relieve the pain. Pain not constant and not definitely located; most of the pain in legs down to ankles. No pain in feet and could not walk or sit. Turning in bed gave sharp pain in back of pelvis; only when on either side did he find comfort. On admission—complaints of pain in pelvis and both lower extremities; consequent inability to walk any distance. Thyroid negative, neurological negative; spine not tender; no deformity or rigidity. Pains considered functional. January 25, 1916—pains vague and irregular, at times severe and frequently absent. On rotation, intense sacral pains; prostate somewhat hard and enlarged. X-ray—slight defect in the outline of the body of the 4th lumbar vertebra not clear. April 16, 1916—very severe pain in both hips; motion left lower limb limited and very painful; knee jerks absent. X-ray, April 20, 1916—defect in 4th lumbar, also 3rd and 5th. Retention of urine and feces developed, also loss of weight. Spine shows no deformity or tumor but has extreme tenderness on pressure over 3d, 4th, and 5th lumbar spine and both sacroiliac joints. Later followed symptoms of cord involvement. Autopsy:—malignant adenoma thyroid with metastases to lumbar vertebrae. Body of 4th lumbar replaced by fleshy tumor mass penetrating through disc to 3rd and 5th lumbar, tumor encroaching on canal though it does not project through the meninges. Hemorrhage of lumbar nerve root.

CASE 6.—01129. F. G. Male, age 63 years. Admitted, August 24, 1916; died, February 9, 1917. Since January, 1916, had pains in left thigh which were constant, but at times so severe that he could not walk. On admission,—lumbar and sacral spine painful on pressure, more marked on left side. Muscular rigidity but no tumor present. Deep and superficial tenderness of left lower extremity; rectal negative. X-ray, August 31, 1916, general carcinomatosis lumbar spine, sacrum and left femur. Autopsy:—carcinoma of prostate, metastases in bones, femur friable, replaced by tumor.

CASE 7.—0591. B. F. Female, age 56 years. Admitted, July 6, 1915; died, July 25, 1915. One and one-half years ago patient fell and was unable to raise herself. Was put in plaster corset for five months. Since March, 1915, was unable to walk. On admission,—marked tenderness dorso-lumbar spine; entire spine rigid; marked lateral curvature at 2nd lumbar. Entire left lung dull. Autopsy:—primary adeno-carcinoma lung, metastases in pleural, liver, adrenal, ribs, vertebrae, glands, suppurative pericarditis, duodenal ulcer, slight compression of cord equina by metastasis at 2nd lumbar.

CASE 8.—01782. B. K. Male, age 40 years. Admitted, June 9, 1918; died, September 9, 1918. July, 1917, cutting, cramplike pain in left inguinal region, radiating to testicle, so severe that patient was unable to walk. Ten months ago pain in left lumbar region, then pain in left axilla, radiating to spine. Pain constant, made worse without cause; no relief from medication or therapeutic treatments. Tenderness over left chest; herpes zoster along course of intercostal nerve.

Teeth extracted, February, 1918. Gave streptococcus viridans in pure culture as did the tonsil. Wassermann negative, spinal fluid negative. X-rays, February 25, 1918,—sinuses, cloudiness of both anterior ethmoids. X-ray of spine unsatisfactory. Considered a pernicious neurotic. For past two weeks pains in right hip, increased by motion. Small swellings over ribs anteriorly and behind ears. On admission,—pains in back, shoulders, hip, stiffness of neck; masses over chest and hip painful on pressure. Loss of weight, fifty pounds in year. Small, hard mass in front of neck, not painful. On examination, patient very sensitive; flexion left thigh causes severe pain, as does any motion. No tenderness of vertebræ or femur. Feeling of cold in right lower extremity. June 28, 1918, prostate negative. Very hard tumor size of nut adherent to fascia and laryngeal cartilage; not painful. X-ray, June 18, 1918,—small diffuse spots throughout bodies of vertebræ and 12th rib. Multiple fractures of ribs. Irregular bone destruction along S. I. joints, pelvis, and left femur. Infiltration of lungs with carcinoma of thyroid. Metastases of bones and lungs.

CASE 9.—0734. F. E. Female, age 56 years. Admitted, November 10, 1914; died, January 1, 1916. Onset, 1911, with pains in thighs. Breast amputated, September, 1913. After one year, recurrent, followed by marked weakness; no muscle atrophy. Could not raise heel off bed. Neurological examination negative. December 24, 1915, fell off a chair, fracturing lower one-third of femur. X-ray showed carcinoma. Autopsy:—ribs, femur, spine showed carcinoma.

CASE 10. 0753. Female, age 45. Admitted, October 1, 1915; died, January 22, 1916. One year ago had pain in left arm, and breast was removed. Then developed pains elsewhere; these grew worse and the patient weaker. On admission,—atrophy, small muscles right hand; painful spots on spine; swelling on lumbar region; bed sore; increased reflexes; later, signs of cord compression. X-ray, October 14, 1915,—metastases show in all bones, best in hips, shoulders, ribs and skull.

CASE 11.—03041. B. B. Female, age 69. Admitted, July 30, 1918; died, November 19, 1920. Five years ago bloody expectoration, ill four weeks. Well for two years, then pain in right foot and leg. Pain beginning in hips and radiating downwards, then pain in both legs, edema of legs. Stiffening and weakness of right hand. Diagnosis:—Mitral regurgitation, arteriosclerosis, chronic arthritis, facial palsy, October 14, 1920, recurrent carcinoma right breast, ulcerations on cuirasse. X-ray:—Marked hypertrophic arthritis of spine, metastases not evident.

CASE 12.—0761. R. R. Female, age 43. Admitted, January 1, 1916; died, February 3, 1916. May, 1915, noticed tumor in breast. Operated in August. Then followed pains in thighs, later in spine, also of piercing character. Pain on pressure along spinal processes. Kyphos

evident and thickened trochanters. X-ray, January 20, 1916,—worm-eaten appearance 11 and 12 D and lumbar vertebrae, also femora. Autopsy:—Dorso-lumbar vertebrae crumble under saw, no definite metastases seen, body of 12th dorsal almost gone, metastases in liver and glands; brain and spinal cord negative.

CASE 13.—02817. H. M. Female, age 43. Admitted, December 9, 1919; died, June 13, 1920. July, 1918, operation right breast. June, 1919, stabbing, right thigh medially, when walking gradually became worse. Last three weeks pain steady in knee and in right hip. Sleeplessness due to pain; five weeks internal strabismus left eye. On admission:—two bony nodules in left parietal region, are not tender. Tenderness of right thigh, cannot lift knee off bed although motions are free. Reflexes normal, no spinal tenderness or deformity. X-ray, December 20, 1919, metastases, skull and right femur, slight erosion at fourth lumbar vertebra. April 11, 1920, irregular bone destruction throughout body of fourth lumbar and both femora where there is periosteal reaction in some places.

CASE 14.—02758. I. K. Female, age 36. Admitted, January 8, 1920; died, May 8, 1920. Four years had mass at suprasternal notch and right supraclavicular fossa which never troubled her. Ten months had mass in right parietal region, never painful. Five months ago stumbled while walking and had severe pains but managed to walk for a month. For increased pain, went to hospital, where cast was applied for fractured femur. On admission:—hard thyroid mass, soft mass at third and fourth rib anteriorly and at parietal, not tender; in plaster cast. January 23, 1920, paralysis of left leg with increased K. J., ankle clonus and Babinsky both sides. February 17, cast removed, decubitus present and signs of complete transverse myelitis. X-ray, January 13, dorso-lumbar spine negative; January 29, extensive bony destruction upper right femur, skull, lower lumbar spine. Carcinoma thyroid, metastases skull, femur, ribs, lumbar spine.

CASE 15.—02873. J. D. Female, age 26. Admitted, January 14, 1920; left, July 28, 1920; died, December, 1920. Five years ago operated, left breast; five months ago pain left hip which interferes with walking. Later, pain in hip less, but pain in lower end of spine; when in bed, pains less. On admission:—complaining bitterly of pain in left thigh with weakness that is progressively worse. X-ray, January 2, diffuse metastatic involvement in pelvis, lumbar spine, skull, lungs; collapse second lumbar vertebra. April 11, large area of bone destruction on upper part of right sacro-iliae and both pubic bones; hips negative. July 8, 1920, no complaints; pain on pressure fourth and fifth lumbar and ribs.

CASE 16:—02811. S. R. Male, age 60. Admitted, January 3, 1917; died, June 11, 1920. March, 1915, total excision of bladder for carcinoma. Later, general weakness and lung signs, no spinal symptoms.

X-ray, February, 1920, pelvis negative, marked lung shadows, slight metastatic changes of the fifth lumbar vertebra.

CASE 17.—02518. Female, age 54. Admitted, May 1, 1919; died, November 24, 1919. May, 1918, noticed lump in breast, marked loss of weight, for three months pain in left eye led to its destruction. On admission:—cancer, right breast, with axillary glands; right upper extremity edematous; August 14, right eye also involved. X-ray, May 13, second lumbar vertebra somewhat collapsed and small area of bone destruction in lumbar spine, sacrum and skull.

CASE 18.—02568. R. R. Female, age 50. Admitted, August 22, 1919; died, January 8, 1920. November, 1917, breast removed; April, 1919, for pain in leg went to hospital, while there spontaneous fracture humerus. On admission:—tumor left clavicle; no glandular involvement; fracture humerus; lower dorsal spine shows sharp kyphos, left gluteal bed sore, neurological examination negative. October 29, 1919, patient rather apathetic and complains of cramps. January 2, 1920, no complaints but weaker. X-ray, November 6, 1919, moderate diffuse bony destruction spine, sacrum, pelvis, femora, scapula, humerus and other bones.

CASE 19.—0X. A. F. Female, age 40. Admitted, October 12, 1920; died, January 1, 1921. Nine years ago breast operated on, one year ago recurrence, operated; for three weeks weakness of legs, unable to walk; swelling of legs. On admission,—carcinoma on cuirasse; reflexes normal, edema left hip, spine shows marked tenderness of 7 dorsal. X-ray:—spine, pelvis, hips, shoulders negative for metastases.

CASE 20.—0X. M. M. Female, age 54. Admitted, December 9, 1920; died, December 10, 1920. Eight years ago lump in breast; operated on April, 1919; well one year, then pain in chest; grew weaker and worse. Five months ago pain more severe; increased weakness and incontinence; one month cannot stand; now transverse myelitis with bed sores and complete paralysis below hips.

CASE 21.—02924. B. K. Male, age 56. Admitted, July 29, 1920; died, September 4, 1920. Eighteen months ago influenza; cough persistent and became more constant. Four months drawing pain right arm and pain right chest anteriorly. August 18, 1920, pain left gluteal region, pain and marked tenderness left sacro-iliac. No symptoms of spine. X-ray, August 4, 1920, beginning bone rarefaction left sacro-iliac and right humerus. Other bones negative. Autopsy:—primary tumor right lung, metastases left lung, ribs, lower spine, direct extension of tumor into superior vena cava.

CASE 22.—02251. J. D. Female, age 56. Admitted, May 22, 1919; died, June 21, 1919. Nine years ago amputation of left breast; one year ago pain across back; absent when lying down; on standing, pain



down thighs and calves. March 6, 1919, tenderness over mid-lumbar, sacrum, and sacro-iliac joints. Diminished power in wasting right thigh. K. J. absent, no tenderness on stretching sciatic. X-ray showed extensive involvement of lumbar and sacral vertebræ. On admission:—inability to walk, pain in back, radiating down both lower extremities. Incontinence, edema lower extremities; slight scoliosis, abdominal negative; axillary glands palpable; mass above sacrum; vertebræ not tender to pressure; sacrum sensitive, paraplegia dolorosa. X-ray, June 18, 1919, pelvis marked rarefaction and destruction throughout entire pelvis, process most marked in the spine. Marked bilateral hilus shadows in the lungs.

CASE 23.—02256. R. B. Female, age 40. Admitted, March 27, 1919; died, June 23, 1919. Ten months ago amputation right breast; three weeks thereafter sudden sharp pain in back of neck, next pain in right shoulder, then in right thigh, so severe patient could not walk. Pain progressed to entire back, abdomen and into left thigh; later, chest and entire body became affected. On admission:—pain all over body, sleeplessness, constipation. On deep palpation back of neck, abdomen, chest painful; axilla free of glands. X-ray, April 18, 1919, marked evidence of small areas of bone destruction throughout bony system, greatest amount in bodies of 10, 11, 12 dorsal.

CASE 24.—01293. Y. D. Female, age 42. Admitted, January 7, 1918; discharged July 8, 1918. April 16, 1916, noticed lump in breast which was operated on in June; then pain in right leg. X-ray showed carcinoma. Pains in right hip and right shoulder; active motion lost due to pain. Right leg one and one-half inches short. February 27, 1917, pathological fracture humerus. Tenderness left of lumbar spine. X-ray, right shoulder, absorption of bone: right hip, fracture at neck; much destruction.

CASE 25.—01291. R. W. Female, age 40. Admitted, June 14, 1917; discharged, July 7, 1917. Two years ago lump in left axilla noticed. Breast operated on one month later; second operation, January 12, 1917. On admission:—pain all over body, especially in both humeri, left knee and back. Local recurrence at breast; both upper extremities edematous. Abdominal negative; shoulders, hips, and spinous processes all painful on pressure; no deformity, slight limitation flexion right hip. X-ray,—spine and shoulders negative; hips, left slight destruction below acetabulum,—right, slight arthritic changes.

CASE 26.—01418. M. R. Female, age 48. Admitted, October 22, 1917; died, October 27, 1917. September, 1915, vomiting attacks. Operated for tumor of left kidney; five months ago sitting in chair, was unable to get up, had pain in dorso-lumbar region. On being helped up was unable to straighten back; four weeks later feet began to swell; could not move feet; sleeplessness from pain in back; last ten weeks lost control of bladder, then, also bowels. On admission:—right but-

tock ulcer, paraplegia, cystitis, metastatic carcinoma dorsal and lumbar spine from left kidney.

CASE 27.—02324. R. S. Female, age 35. Admitted, June 17, 1919; died, July 28, 1919. Nine months ago severe pain in region of stomach, and headache. Constant pain radiating down sides of legs. Examination shows palpable mass attached to liver; spinal column very tender to touch at 8th dorsal and below. June 20, complains bitterly of pains in back; June 26, incontinence, pain all over body. Autopsy:—carcinoma pancreas, liver, and stomach, involving spinal column.

CASE 28.—C2. S. T. Female, age 40. Admitted, June 17, 1920. Four and one-half months ago while stooping found that she could not lift her lower extremity and the next day her right. Difficult walking, weak; later, stabbing pain and burning over entire back; continuous sticking pain in lower part of right chest. May 12, 1920, operation, breast, for inoperable carcinoma. Angulation to left at 3rd and 4th dorsal. On admission:—weakness, arms and legs, reflexes increased. June 25, 1920, local pain in first and second lumbar; no sensory changes. January 16, 1921, no pains now in back; spine somewhat sensitive; gradual kyphos. X-ray, June 21, 1920, rarefaction of bones of spine, rather indefinite.

CASE 29.—C2. S. L. Female, age 42. Admitted, September 22, 1920. Breast operation two years ago; four months ago feeling of cold all over body; three months ago edema of left arm, weakness, left facial palsy, left knee swollen and tender. On admission:—local recurrence, left knee swollen and tender. X-ray, October 4, 1920, left tibia, fibula, femur show a few spots of rarefaction. Moderate irregular rarefaction throughout upper sacrum.

CASE 30.—C3. J. S. Male, age 57. Admitted, April 21, 1920. December 29, 1919, suprapubic operation for bladder stone. Adenoma with carcinomatous changes, also carcinoma prostate. June 19, pain left loin downward to thigh,—urinary disturbance. On admission:—weakness, especially legs, constipated, pain side of thigh, inoperable prostate carcinoma. July 7, 1920, pain left femur, local tenderness. January 17, 1921, spine tender at places, but can walk. X-ray, July 15, 1920, cervical spine negative. August 10, 1920, small areas destruction third cervical. Extensive diffuse rarefaction upper part of femur.

CASE 31.—W1. S. G. Male, age 88. Admitted, July 23, 1920. About six months ago weakness of both legs, progressive until unable to stand, followed in one month by inability to urinate. Three months ago prostatectomy for enlarged prostate. On admission:—inability to stand or walk, no bladder or rectal disturbance, no pain, paraesthesia or swelling of extremities. Later, there developed signs of local cord lesion with a zone of hyperaesthesia across chest and paraesthesia

of left lower extremity more than right. Distinct depression at height of tenth dorsal vertebra, slight sensitiveness over entire spine. Hard nodule region of prostate now felt. X-ray:—Arthritis of second and third lumbar, otherwise negative.

CASE 32.—E2. E. O'G. Female, age 27. Admitted, October 4, 1920. September, 1918, breast amputation. October, 1919, to hospital for back complaints, pain and weakness in lumbar region. Spinal corset gave no relief. Several x-rays were negative; January, 1920, at another hospital, x-rays diagnostic. Radium treatments given. June and July, well again. On admission:—complaint for sixteen months of stiffness in back and pains in back radiating down thighs. Cannot walk, but can stand. X-rays show very marked bone destruction of pelvis and spine. January, 1921, free from pain and has no tenderness on local pressure of spine and pelvis; sensorium intact; distinct depression fifth dorsal vertebra and kyphos upper dorsal. Increased reflexes and spasticity of legs; marked loss of weight, signs of cord compression.



MORPHOLOGIC APPEARANCE OF CANCER  
CLINICALLY CURED BY RADIUM  
AND ROENTGEN RAY\*

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NEW YORK

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The reports on the result of surgical treatment of cancer cases as well as the more recent reports on radium and Roentgen-ray therapy of the disease abound in expressions "radical cure," "clinical cure" and "improvement." It is appropriate, therefore, to preface the analysis of the cases presented for this study by a correct definition of these terms.

A surgical statement that a cancer case is radically cured implies that the patient is alive and free from the disease from three to five years after the operation. The probable ultimate result of a radical operation may be inferred among others from the following study of a French surgeon, Heurtaux. During a period of thirty years he operated in 341 cases of carcinoma of the breast; 284 cases could be traced for long periods of time, and of these patients, 43.3 per cent. remained well four years after the operation and should consequently be considered radically cured. Four years later, or eight years after the operation, only 16.9 per cent. remained well and free from a recurrence. Ten years after the operation only 12.32

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\* From the Department of Cancer Research of the Montefiore Hospital and Home.

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per cent. remained well, fifteen years after the operation 8.1 per cent., and twenty years after the operation only 2.46 per cent. remained free from a recurrence. A recurrence of cancer, no matter how late after an operation, indicates that some tumor tissue was left behind somewhere in the organism at the operation. A radical operation for a malignant tumor means a complete eradication of all tumor tissue from the organism. An analysis of Heurtaux's writings, and many other similar publications, thus shows that in by

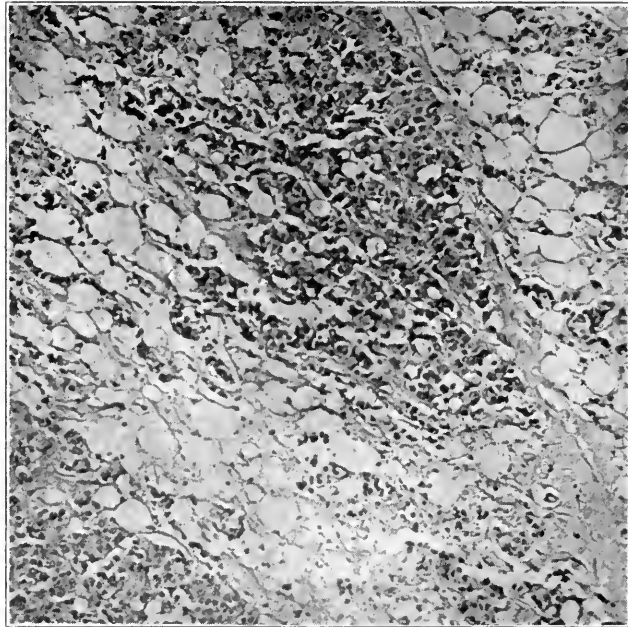


Fig. 1 (Case 1).—Scirrhous carcinoma of the breast.

far the greatest majority of cases of cancer the best surgical methods of treatment do not completely eradicate the disease and consequently do not induce a radical cure of the disease. Most frequently, then, surgery only postpones a recurrence and thus prolongs life. It is quite legitimate, nevertheless, to consider such a result a clinical cure, since the patient remains clinically well for a longer or shorter period of time, and the presence in the organism of the remnants of

the malignant tumor cannot be detected by any means at our disposal. Furthermore, a clinical cure takes place even when the malignant tumor does not entirely disappear, but loses the characteristics of its malignancy, ceases to grow and invade the surrounding tissue, behaves clinically like a benign tumor and retains these characteristics for a sufficient length of time. To recapitulate: A clinical cure of cancer means a gross destruction or diminution of the size of the primary tumor with disappearance of symptoms and a well being continued for a sufficiently long time to preclude the possibility of a spontaneous remission of the disease.

An "improvement," "palliation" or "palliative improvement" must be considered the alleviation of distressing symptoms without any inhibition of the development and growth of the malignant tumor. A tracheotomy for the relief of dyspnea in carcinoma of the larynx, gastrostomy for relief of obstruction in carcinoma of the cardia, gastro-enterostomy in carcinoma of the pylorus, and colostomy in carcinoma of the colon produce such a palliative improvement, which may be followed by increase of weight and strength and temporary well being of the patient. The action of radium and Roentgen rays in arresting hemorrhage, foul discharge and relieving pain in far advanced inoperable cancer cases also induces thereby a palliative improvement.

One of us<sup>1</sup> recently reported on several cases of inoperable carcinoma and sarcoma which remained clinically cured for a number of years by the aid of radium and Roentgen-ray therapy. The number of similar cases reported by other investigators is so great, and the therapeutic action of these radiations is so frequently satisfactory under correct and uniform conditions, that the specific action of the rays on malignant tumors does not require any further discussion. The fact that in the vast majority of cases of malignant tumors which undergo the radium and Roentgen-ray treatment a palliation or a clinical cure and not a radical cure is obtained does not detract anything from the value of the method.

The clinical effect of the radium and Roentgen rays on malignant tumors is accompanied in the great

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1. Levin, Isaac: Surg., Gynec. and Obst., 1915, **21**, 374.

majority of cases by distinct morphologic changes in the tumor tissue. As a general rule, it may be stated that tissues consisting of less differentiated, younger cells, cells in a state of active proliferation, are most deeply influenced by the rays, and that consequently there is selective action of the rays on the actively proliferating tumor cells, as compared with the normal organ cells. The first morphologic changes which occur in carcinoma or sarcoma tissue under influence of radium and the Roentgen rays are observed

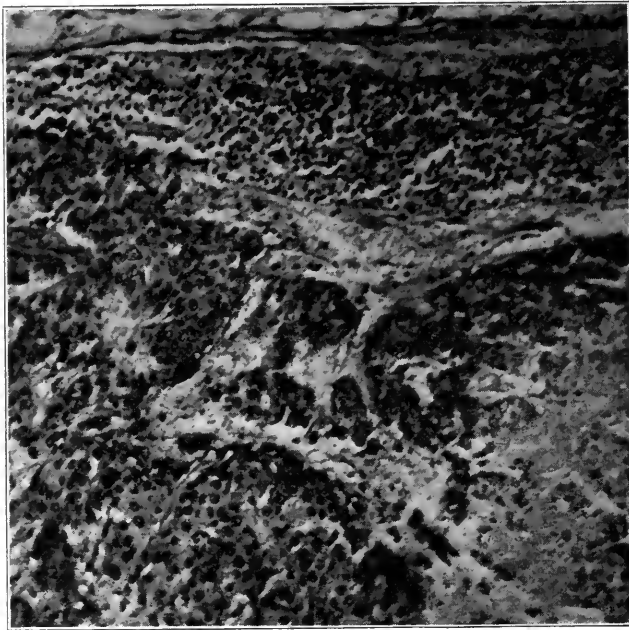


Fig. 2 (Case 1).—Metastatic carcinoma of a lymph gland.

in the tumor cells themselves, and are manifested by the vacuolation of the protoplasm, pyknosis of nuclei, karyolysis, and ultimately complete necrosis of the cell. These cellular changes are accompanied by a round cell infiltration which replaces the destroyed cancer cells. Subsequently this round cell infiltration is changed into dense sclerotic connective tissue poor in blood vessels. This connective tissue formation may become very extensive, surround islands of can-



cer cells, and assist in the destruction of the latter. Indeed, this new connective tissue formation is the most generally observed morphologic change in the tumor. Some observers even maintain that this connective tissue formation is the only direct effect of radiation, while the destruction of the tumor cells is secondary and is due to lack of nutrition. However, this opinion is not borne out by facts. The first morphologic change noted is always the destruction of the tumor cells, and the connective tissue appears only subsequently. Moreover, in certain conditions—for instance, rodent ulcer of the skin—the epithelioma cells disappear and the ulcerated area is covered with skin epithelium without any formation of connective tissue. The assumption, on the other hand, that the formation of connective tissue is secondary to the accumulation of dead tumor cells and is analogous to formation of connective tissue around foreign bodies and particles of dead matter is also hardly tenable. Were this connective tissue formed only by the stimulus of the dead tumor cells, then the radiations would dissolve it subsequently as easily as it dissolves a keloid, for instance. However, this does not take place, and the amount of the peculiar sclerotic connective tissue usually increases with subsequent radiations.

A case of carcinoma of the sigmoid with metastatic dissemination in the peritoneum previously reported by one of us<sup>1</sup> demonstrates the importance and extent of this connective tissue formation. An exploratory laparotomy was done on the patient which revealed a carcinoma of the sigmoid and a peritoneal dissemination with minute metastatic nodules. The case was declared to be inoperable and the tumor was not removed. The patient was treated with massive doses of Roentgen rays for six months; subsequently the patient died from an acute intestinal obstruction. At the necropsy there were found in the peritoneal cavity several loops of the small intestine adherent by old adhesions to the posterior surface of the tumor mass in the sigmoid. The peritoneum was studded with numerous white plaques, varying in size from 1 to 5 mm. in diameter. Microscopic examination of a section taken through two loops of the small intestine that were firmly bound together by adhesions showed that the latter consisted of a thick layer of connective

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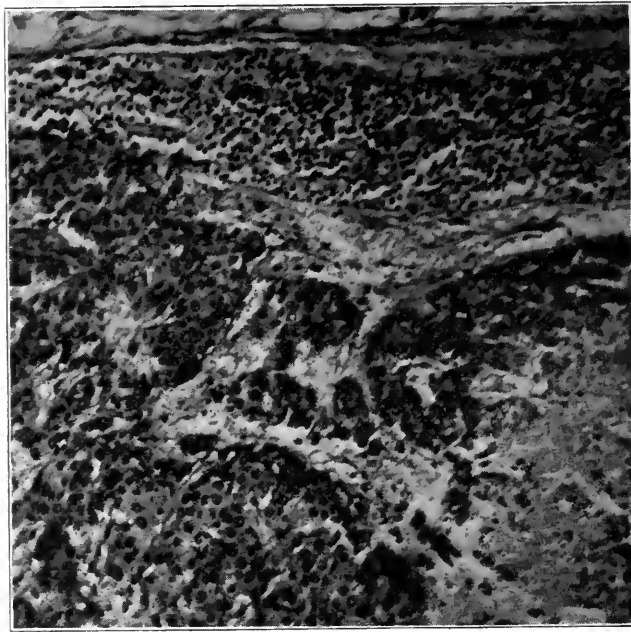


Fig. 2 (Case 1).—Metastatic carcinoma of a lymph gland.

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tissue containing occasional nests of tumor cells. The peritoneal nodules were composed of dense connective tissue, with occasional minute groups of tumor cells. The amount of connective tissue in these peritoneal nodules of carcinoma was entirely out of proportion to the number of carcinoma cells present. On the other hand, the peritoneal endothelium of the sections of the wall of the small intestine adjacent to the plaques was normal and showed no connective tissue formation.

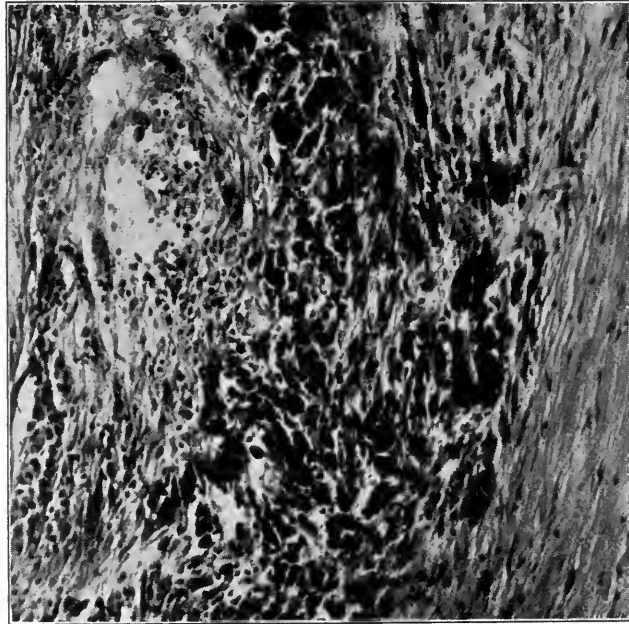


Fig. 3 (Case 2).—Melanotic cancer, primary tumor, before treatment.

The source of the new connective tissue formed under the influence of the radium and Roentgen rays must be looked for either in the stroma of the tumor or in the round cell infiltration that closely follows the destruction of the tumor cells by the radiations. It may be stated then that while the destruction of the tumor cells is the primary phase and the formation of new sclerotic connective tissue a secondary, it is at least as important a phase in the morphologic changes which

take place in malignant tumors under the influence of radium and Roentgen rays. Furthermore, the microscopic study of this case of carcinoma of the sigmoid indicates the possibility that the proliferating capacity and the consequent clinical malignancy of a tumor may be inhibited under the influence of the radiations without the presence of any apparent morphologic changes in the tumor tissue. The deeper portions of the sigmoid tumor, as well as a certain number of the peritoneal plaques, showed morphologically unchanged carcinoma cells. Nevertheless, in over six months not a single one of the minute nodules found at the operation developed into a discrete secondary tumor, and the primary sigmoid tumor did not increase in size during the time.

The following series of cases, observed recently by us, present a similar condition of clinical cure without any apparent morphologic changes in the tumor tissue:

CASE 1.—Mrs. W. Y., aged 40, was admitted to the Montefiore Hospital in 1906 suffering from bronchial asthma and emphysema. In August, 1915, a hard mass the size of a hen's egg was discovered in the outer margin of the right breast. The skin was adherent to the tumor, and there were enlarged glands in the right axilla. A clinical diagnosis was made of carcinoma of the breast with the involvement of the axillary glands. The general condition of the patient precluded any operative interference, and she was treated by local application of radium to the breast and axillary glands and Roentgen-rays through the chest wall. The breast tumor and the gland at first diminished somewhat in size and then remained stationary. Seventeen months later the patient died from her pulmonary condition. A complete necropsy was performed by Dr. B. S. Kline. A minute search was made for possible metastases, but none were found anywhere in the organism. The microscopic examination of the tumor of the breast showed a scirrhus carcinoma, and the lymphatic glands of the axilla were filled with solid carcinoma. Figures 1 and 2 show that morphologically both the primary tumor and the metastases in the lymph glands appeared quite malignant and did not show any changes characteristic of radiotherapy. Nevertheless, nearly a year and a half after the condition was discovered, no dissemination or distant metastases were found anywhere in the organism.

As a rule, a patient with carcinoma of the breast with the involvement of the axillary glands, if left untreated, dies in less than a year and a half from a general dissemination of the carcinoma. It is thus quite evident that in the case reported here radium

and Roentgen ray therapy inhibited the further growth and dissemination of the carcinoma tissue and transformed it, as it were, into a biologically and clinically benign type of a tumor, though it did not change its morphologic appearance.

CASE 2.—Mrs. B. K., aged 40, developed a pedunculated tumor the size of a small orange on the skin of the right supraclavicular region. The tumor was removed in March, 1915, with the pedicle. There was left after the operation an ulcerated area 1 cm. in diameter that did not heal. The microscopic examination (Fig. 3) of the tumor showed it to be a

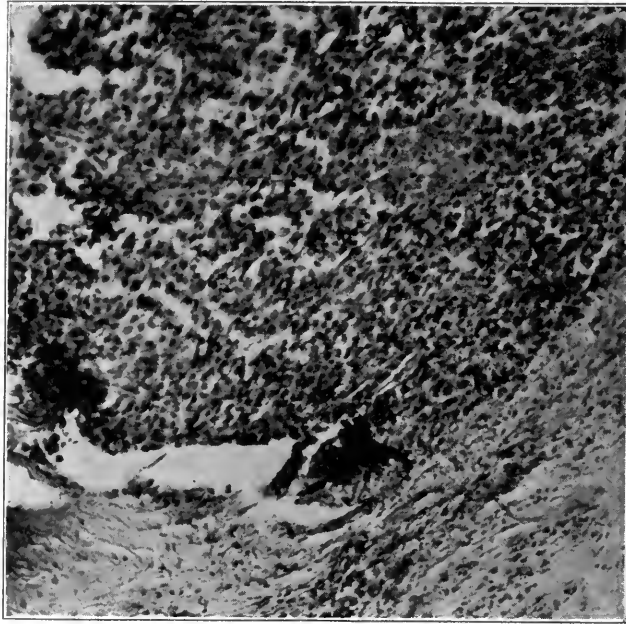


Fig. 4 (Case 2).—Melanotic cancer of the lymph gland twenty months after the beginning of the treatment.

melanotic cancer. The case was then referred to one of us for radium and Roentgen-ray treatment. On examination there was observed the ulceration described above and an enlarged supraclavicular lymph gland about three-fourths inch long. Under the influence of the ray therapy, the ulcer healed and the gland at first diminished somewhat in size and then remained stationary. At present, two and one-half years after the beginning of the treatment, the patient is clinically perfectly well, and no metastatic tumors have developed any-

where. Melanotic cancer is an exceedingly malignant condition, and the average life of the patient is not more than two years. Coley and Hoguet,<sup>2</sup> who made an exhaustive study on the subject, state that the melanotic cancer in the cervical glands is especially malignant, causing death in a short time. In October, 1916, twenty months after the beginning of the treatment, the supraclavicular gland was excised for diagnostic purposes. The microscopic examination (Fig. 4) of the gland showed a morphologic picture identical with the one found in the primary tumor before the initiation of the treatment. Nevertheless, as stated above, at present, eight months after the second operation and two years and three months after the first, the patient is perfectly well and did not develop any secondary tumors anywhere. Here again the radiotherapy inhibited the proliferating power of the cancer cells and arrested the growth of the tumor without having produced any apparent morphologic change.

CASE 3.—Mr. B. G., aged 51, was operated on in December, 1915, for adenocarcinoma of the ascending colon. The tumor was radically removed and a right colostomy performed. In February, 1916, the patient was admitted to Montefiore Hospital. On admission, no recurrence of the carcinoma was found anywhere. In July, 1916, an attempt was made to close the colostomy wound by the aid of clamps, but the operation was discontinued since a recurrence was discovered at the intestinal bridge of the colostomy opening. There was felt a hard tumor mass about a cubic inch in size. The outer surface of the tumor consisted of an ulcerated area about three-fourths inch in diameter. A small piece was excised for examination, and showed microscopically an adenocarcinoma (Fig. 5). For the last ten months the patient has been undergoing Roentgen-ray treatment. He is clinically well, the tumor did not increase in size, the ulceration appears to be partly healed, and no secondary tumors or metastases developed anywhere. Recurrences in intestinal carcinoma are generally malignant, and disseminate all over the peritoneum and kill the patient very rapidly. Recently another piece was excised for examination, and the result of the microscopic study of this later specimen (Fig. 6) is very instructive. There is no direct evidence of any extensive degeneration of the cancer cells or excessive formation of new sclerotic connective tissue characteristic of radiated malignant tumors. But, unlike Cases 1 and 2, the two specimens of this case removed before and after treatment do show a certain morphologic difference. While the specimen taken before treatment shows a perfectly characteristic picture of adenocarcinoma in every field, the specimen obtained after treatment is not so characteristic, and a great many of the tubules resemble more a benign adenoma than an adenocarcinoma. These findings are somewhat difficult to explain. It is possible that the superficial, more malig-

2. Coley, W. B., and Hoguet, J. P.: *Ann. Surg.*, 1916, **64**, 206.

nant part of the tumor was destroyed under the influence of the rays. The partial healing of the ulcerated surface coincides with this assumption. The deeper portions were then inhibited by the Roentgen ray in their further malignant transformation. In any event, a clinical inhibition is quite evident in this case as well.

We have been unable to find in the literature any description of similar cases in which a clinical arrest of disease was accompanied by a complete absence of

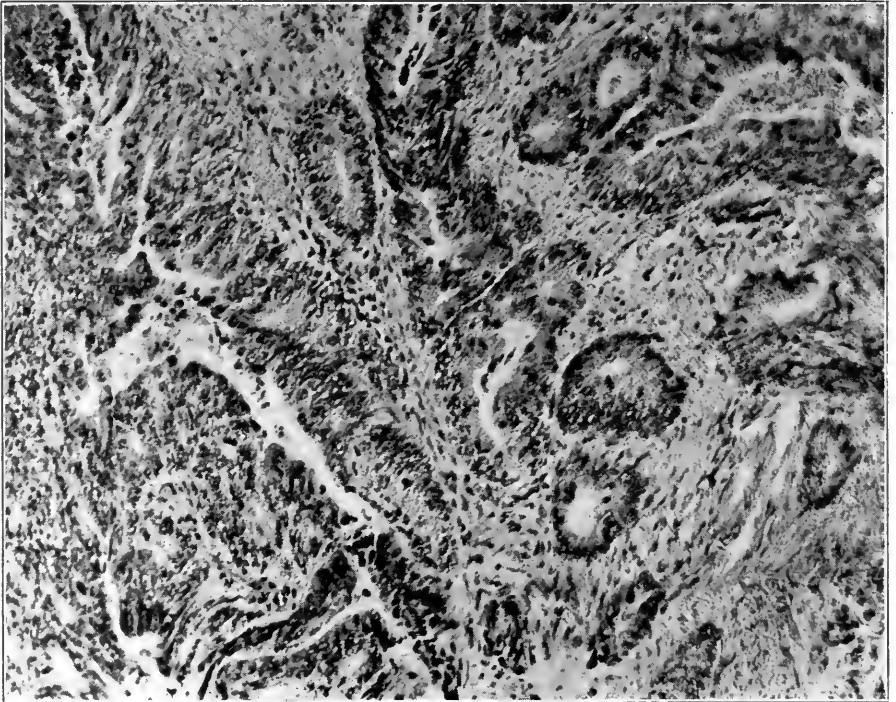


Fig. 5 (Case 3).—Adenocarcinoma of the colon, recurrent, before treatment.

morphologic changes. Morson,<sup>3</sup> in his description of the various changes which occur in malignant tumors on exposure to the gamma rays of radium, states that there may take place a loss of the reproductive function of the cancer cell, but he does not illustrate this condition in any of his cases. On the other hand,

3. Morson, A. C.: *Brit. Jour. Surg.*, 1915, 2, 354.



there is a good deal of experimental evidence that elucidates the clinical and morphologic phenomena described in this presentation. Von Wassermann<sup>4</sup> reported in 1914 the results of his experiments on the action of radium on small pieces of mouse carcinoma in vitro. He has shown that the cells remain alive, but the pieces do not grow when they are subsequently inoculated in a healthy mouse. He concludes that the rays act directly on the cancer cells. However, they do not kill the cells, but impair the genuceptors or the proliferating apparatus, and as a result inhibit the formation of new cells. The actual death of the cancer cell and disappearance of the tumor is produced either through the aging of the remaining cells or through the cytolytic powers of the organism. Therefore, the rays act selectively on tissues, the cells of which are rich in genuceptors and proliferate rapidly. This hypothesis of von Wassermann fits in very well also with the frequently observed clinical fact that a malignant tumor may continue to diminish in size weeks after the ray treatment was discontinued. In a recent publication on the effects of radium on tissue growth in vitro, Prime<sup>5</sup> reports very similar results. He observed that radium injures the nucleus of the cells growing in animal plasma, so that it prevents further formation of mitosis. On the other hand, it does not injure the life and functions of the cell. For instance, the outwandering of the cells from the main mass of the tumor in the culture due to ameboid motion continues with the same rapidity as in the nonradiated control cultures. The beating of a piece of a heart muscle placed in the plasma culture continues for the same length of time in the radiated as in control cultures. Identical results were obtained by Halberstädter,<sup>6</sup> who studied the action of the radium rays on trypanosomes in vitro. The effect of the rays consisted in the inhibition of the infectivity of the parasites; that is, they lost their power to proliferate when introduced into a new host after having been radiated in vitro. On the other hand, the motility of the trypanosomes is not impaired by the action of the radium.

4. Von Wassermann, A.: *Deutsch. med. Wchnschr.*, 1914, **40**, 524.

5. Prime, Frederick: *Jour. Cancer Research*, 1917, **2**, 107.

6. Halberstädter, L.: *Berl. klin. Wchnschr.*, 1914, **51**, 252.

Thus the clinical investigations reported in this presentation as well as experimental studies show that the radium and Roentgen rays may impair deeply the proliferating power and consequently the clinical malignancy of cancer cells without producing any



Fig. 6 (Case 3).—Adenocarcinoma of the colon after treatment.

change in the morphologic appearance of the tumor. Indeed, it is quite probable that the first effect of the rays on every malignant tumor consists in the inhi-

bition of the proliferating power, in the *sterilization*, as it were, of the cancer cells. The degeneration and destruction of the cancer cells and the formation of the sclerotic connective tissue takes place subsequently, under the influence of the rays. Moreover, this cell degeneration and cell death may not be due directly to the action of the rays, but takes place in the natural course of the life cycle of the cancer cell. This cycle consists of youth, or period of development; maturity, or period of function; and the senility, or period of degeneration, which gradually leads to death. In parenchymatous organs, like the liver and the kidney, the first period is usually completed during embryonic life or at very early age. The second period continues through the whole life of the organism, and the third period is attained at the old age of the organism or near its death. The life of an individual cancer cell, on the other hand, is very short. It changes rapidly from an embryonic into an adult and then immediately into an aged, degenerated cell, and this process takes place continually irrespective of any extrinsic aid. But in a malignant tumor the majority of the cancer cells are quickly rejuvenated before they reach senility through the fact that each cancer cell changes into two young daughter cells. When the rays arrest this proliferation, then the cancer cells without any further outside aid mature and degenerate. It is interesting to note in this connection that the life of the epithelium of the skin or testicle is nearly as short as the one of the malignant tumors, and the rays act on these organs as specifically as they do on malignant tumors.

The importance of this observation is twofold. In the first place, the morphologic appearance of radiated tumor tissue is not an absolute criterion of the therapeutic effect produced by the action of the rays on the tumor. Positive finding of the changes described above as characteristic of the action of the rays is an indication of a therapeutic result. Negative findings, on the other hand, do not preclude the possibility that the tumor was influenced by the rays. Radiated and nonradiated carcinoma tissues may have the same microscopic appearance, and still the former tissue is sterilized and may have lost to a great extent its power of proliferation and consequently its clinical malignancy. In fact, the same holds true for

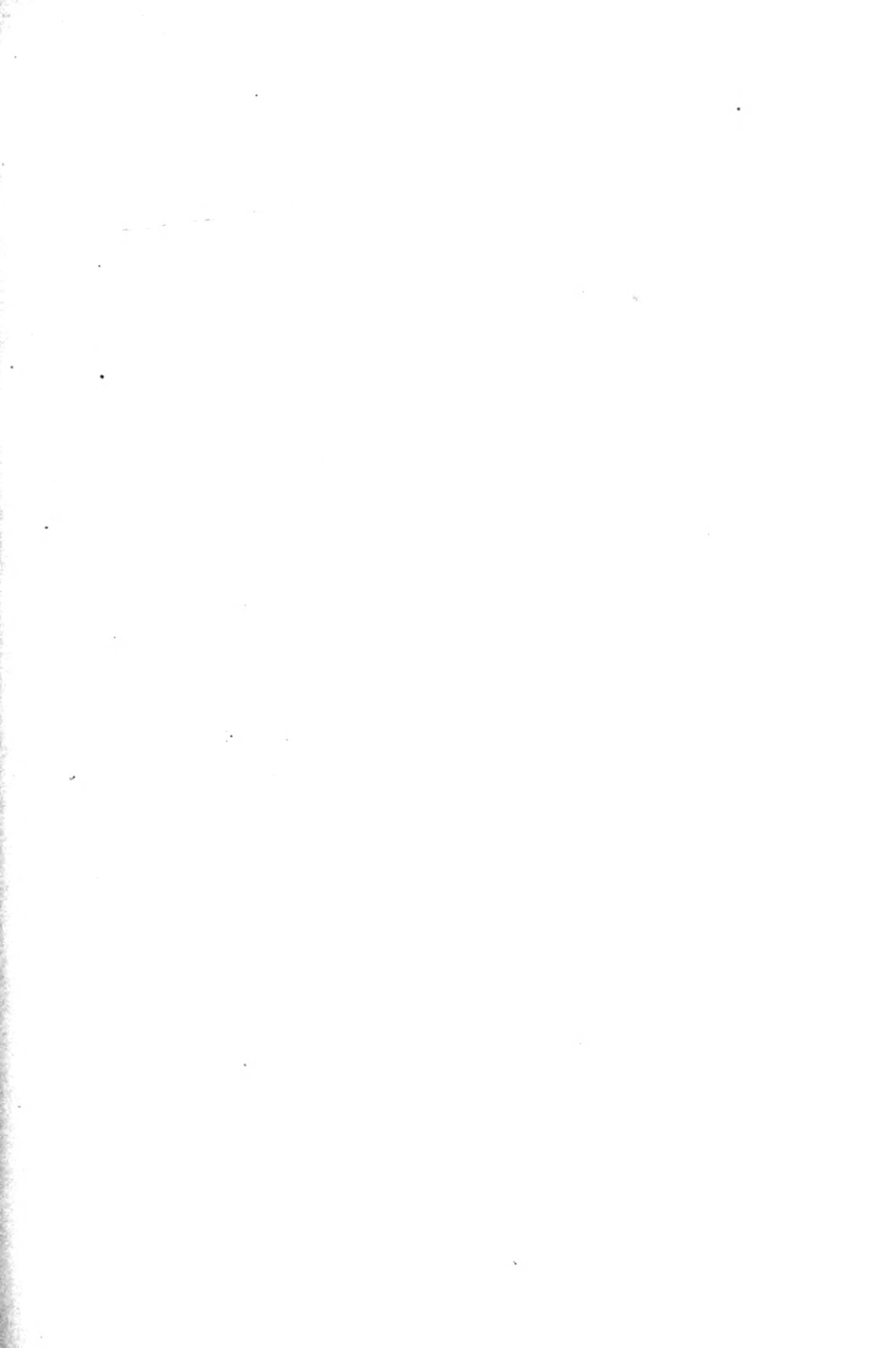
various malignant tumors without any relationship to radiotherapy. An epithelioma may present the same microscopic picture whether it belongs to a comparatively benign, slowly growing ulcer of the face or to a highly malignant epithelioma of the lip. The second point of great practical importance to be derived from this investigation is that the radium and Roentgen rays are capable in a certain number of cases of sterilizing or inhibiting the malignancy of a tumor without destroying it. It is imperative, therefore, to subject every malignant tumor to treatment by the rays, before the performance of the radical or partial operation. The same holds true of postoperative treatment. The rays may sterilize and inhibit the proliferation of the remaining cancer cells, even if they do not destroy them outright.

119 West Seventy-First Street.—2051 Fifth Avenue.

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**THE PROGNOSTIC AND THERAPEUTIC SIGNIFICANCE OF  
SKELETAL METASTASES IN CARCINOMA OF THE BREAST\***

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THE operative procedures for carcinoma of the breast as elaborated by Willy Meyer and Halsted in the United States, Rotter in Germany, and Handley in England, increased considerably the chances for a radical cure of the disease. Indeed, in its early stages, according to the statistics of Halsted, fully 85 per cent. of the cases remain well for the period of three years after the operation. Nevertheless, even to-day the ultimate results obtained with the most radical methods of surgical treatment of carcinoma of the breast are far from being satisfactory. The reason for this lies in the difficulty in having the patients submit to the operation in the early stages of the disease.

It is impossible to form a perfectly correct estimate of the true therapeutic value of the radical amputation of the breast for carcinoma, since in the majority of the publications the authors do not state the percentage of cases which were considered entirely inoperable and therefore were not submitted to any surgical treatment. It is self-evident on the other hand, that the differences in the conceptions of the operability of the cases influence to a great extent the postoperative results. Nevertheless a fairly accurate idea of the results may be formed from an analysis of the recent publications. In the years 1907-1908 there appeared a number of publications with reports of a decade of work with Halsted's and similar methods of radical operations for carcinoma of the breast. Chart I, taken from Halsted's<sup>1</sup> publication, may serve as an example of the results obtained.

CHART I

	Cases	Cured	Per cent.	Cured 3 years	Per cent.
Axilla and neck negative .....	60	45	75	51	85
Axilla negative, neck negative....	110	27	24.5	34	31
Axilla and neck positive.....	40	3	7.5	4	10
Total .....	210				

\* Read at the meeting of the Section on Surgery of the New York Academy of Medicine, November 3, 1916.

Halsted reports in all on 293 cases. Eighteen cases could not be traced and 65 cases had only palliative operations. The remaining 210 cases are divided into 3 groups. The first group consists of early cases in which there is no involvement of the lymphatic glands. In the second group, there are placed the advanced cases with the involvement of the axillary glands, and in the third group the far advanced cases with the involvement of both the axillary and neck glands.

Of the 60 cases of the first group, 51 cases, or 85 per cent., remained well three years after the operation. It is remarkable to note in this connection that even the cases of the Johns Hopkins Hospital, notwithstanding the active educational propaganda carried out by Bloodgood, only 20 per cent. of all the cases reported were in the first group, or in the early stages of the disease. It is probable that were the cases in which even a palliative operation was refused added to the report, then the percentage of the early cases would have been even smaller.

CHART II

Group	Series	Number of cases operated	Number of cases cured	Per cent.
I	I	14	11	78.5
	II	7	6	84.7
II	I	68	20	29.4
	II	25	8	32
III	I	7	0	0
		5	0	0

Chart II presents a very interesting analysis of 200 cases operated upon by Steinthal.<sup>2</sup> He divided 126 cases which were followed up in 3 groups, similar to those described by Halsted. Each group is again divided into 2 series. The first series of cases were operated by the old methods, and the second series by the modern radical methods. The analysis of his material shows that while in the first group, or the early cases, the radical operation produced better results than the old operations, the difference in the results in the advanced cases is not so marked. In the third group no advantage was obtained from the radical operation, either by Steinthal or Halsted, though the latter reports that 10 per cent. were cured, while all the cases of Steinthal in this group died, notwithstanding the operation. Thus the more advanced the disease, the smaller is the probability of obtaining permanent results, even from the most radical surgical treatment. In his latest publication Steinthal expresses the opinion that the increase in the percentage of cured cases is not due to the improvement in the operative technic, but to the earlier recognition of the disease.



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The limitations of the surgical treatment of carcinoma of the breast are due to the following reasons: R. R. Greenough, C. C. Simmons and J. D. Barney<sup>3</sup> have shown that 52 per cent. of the cases in which the operation fails do not show any local recurrence in the operative field, but only metastases in distant regions. In these cases the removal of the local growth was complete, and the metastases were either formed before the operation, or else a tumor embolus was carried away from the primary tumor in the course of the operation. In either event the extent of the operation could not influence the final result. Thus it is self-evident that in the advanced cases which represent three-quarters of all cases submitted to the operation, the probability of the existence of a metastasis before the operation, and of a consequent failure of even an ideal operative method, is great.

Handley<sup>4</sup> attempts to prove that embolism has no significance in the formation of metastasis of carcinoma of the breast. According to his conception, metastasis is formed by a process of "lymphatic permeation." The tumor cells grow along the lymphatic vessels until they reach the nearest lymph-glands, and from these glands the cells enter the next lymphatic vessel. This process is continuous, and the appearance of an apparently isolated tumor nodule is due to the fact that a perilymphatic fibrosis destroys the permeated lymphatic vessels which form the lines of communication. The formation of metastases in distant organs Handley ascribes to the proliferation of cancer cells which escape from the subserous lymphatic plexuses into the serous cavities, pleura, or peritoneum. The cells are then distributed through these cavities under the influence of gravity and of visceral movements and implanted on the serous surface of the viscera. As a proof of this contention he cites the fact that parts of the skeleton distal to the elbow and knee-joints usually escape cancerous invasion. Now, in the first place Case VII shows skeletal metastases distal to the elbow (Fig. 9). Moreover, it is impossible to conceive even on the basis of Handley's theory how a distant metastasis without a local recurrence after an operation occurs, unless the transport of the cancer took place before or during the operation.

CHART III

Years after operation patients are alive	Number of cases	Per cent.
4	123	43.20
8	48	16.9
10	35	12.32
15	23	8.1
20	7	2.46
	329	

Similar conclusions must be drawn from the analysis of Chart III obtained from the report of a French surgeon, Heurtaux.<sup>5</sup> He operated during the 30 years previous to the date of his report on 341 cases. The operation consisted in the removal of the breast and the axillary lymphatic glands without the disturbance of the pectoral muscles. Though his operation is not as thoroughly radical as Halsted's, 43.3 per cent. of the 284 cases which could be traced remained well 4 years after the operation. This remarkable result may be partly due to a special selection of cases for the operation, but what makes the investigation of Heurtaux of the greatest value is the fact that he watched and controlled his patients for 30 years. He was thus enabled to estimate the ultimate results at long intervals after the operation, and as Chart III shows twenty years after the operation only 2.46 per cent. of the cases remained alive and free from the disease. While there are many reports in the literature of isolated cases of late recurrence of carcinoma of the breast, Heurtaux is the only investigator who showed the remarkable frequency with which these late recurrences take place.

Thus the analysis of the cases of Steinthal and Heurtaux demonstrate clearly two facts in relation to the true value of the radical amputation of the breast for carcinoma. In the first place in advanced cases, the result of the radical operation is not better than the results of simpler surgical procedures, furthermore in the greater part of the cases which are apparently cured 3, 4 and 5 years after the operation, the disease recurs at a later date. This latter phenomenon is due in over half of the cases, not to a local recurrence of the disease, but to metastases in distant regions.

Now, carcinoma of the breast metastasizes most frequently in the lungs, bones and the liver. The involvement of the latter organ is probably due in accordance with the theory of Handley to a lymphatic permeation, *i.e.*, a local outgrowth from a neighboring region. Metastasis in the liver occurs usually late in the course of the disease and is secondary to an extensive local recurrence and metastases in the lungs or bones. The formation of metastases in the latter organs is undoubtedly due, as the writer stated in several publications,<sup>6</sup> to an embolic transport of cancer tissue before or during an operation and may take place without a local recurrence. The development and the course of metastases in the lungs is usually quite rapid and is accompanied by early clinical symptoms indicative of the condition. The metastases in the bone are apparently the most frequent cause of the late recurrence in carcinoma of the breast. The condition may con-

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tinue for a long time without causing any symptoms, and when at an autopsy metastases are found, both in the bones and in many other organs, it is highly probable that the latter appeared subsequently to the formation of the skeletal metastases. The fact that E. Kaufman<sup>7</sup> found skeletal metastases in the bones in 52.3 per cent. of the cases that died of carcinoma of the breast is a true indication of the frequency of the condition.

### PRE-OPERATIVE DIAGNOSIS OF SKELETAL METASTASES

A radical operation for carcinoma implies an attempt at complete eradication of all cancer tissue within the organism. While a radical amputation of the breast is not accompanied by a high postoperative mortality, it is nevertheless a severe operative procedure. It is usually followed by a prolonged after-treatment, and frequently by disability, pain and swelling of the arm. Moreover, the thorough clearing out of the axilla may be followed by a dissemination of cancer tissue into distant organs and subsequent formation of metastases. In view of all this, it is imperative to ascertain before the operation whether there are any metastases present in any distant region of the organism of the patient.

Metastases in the lungs and in the liver as a rule produce clinical symptoms and are easy to recognize. Skeletal metastases, on the other hand, as stated above, may continue for a long time without causing any symptoms whatever. The frequent reports of pathological fracture occurring in patients who apparently enjoyed previously perfect health, and in whom only the accident revealed the presence of carcinoma, bear out this assertion.

The mechanism of the development and growth of skeletal metastases, as will be shown later, shows the reason for the late development of the clinical symptoms, but in any event, it is certain that a case of carcinoma of the breast with the involvement even only of the axillary glands may harbor metastases in the bones which do not manifest themselves in any way. The only method by the aid of which many of such metastases may be detected is the röntgenographic examination of the skeleton.

The röntgenogram usually reveals a central focus of bone destruction which is evidently replaced by carcinoma tissue. It must be admitted that a negative finding is not conclusive, since the tumor nodule in the bone may be too small and has not destroyed as yet a sufficient amount of the bone tissue to present a shadow on the plate, but a positive result makes the diagnosis of the condition certain. In

view of the importance of the subject it is remarkable how little attention is being paid to this method of diagnosis of skeletal metastasis.

As stated above metastases, usually in the bones, may be present at the time of the operation in 52 per cent. of the advanced cases of carcinoma of the breast, even with involvement only of the axillary glands. It is therefore imperative that in every advanced case, or better still, in every case of carcinoma of the breast, a röntgenographic examination be made of the skeleton before the operation. If it is too expensive or difficult to explore the whole skeleton, then those parts should be examined in which metastases most frequently occur, namely the spine and the femurs.

#### REPORT OF CASES

At the service of the writer in the Montefiore Hospital, the röntgenographic examination of the skeleton of all cases of carcinoma of the breast is a routine procedure. During the past three years the writer observed 10 cases of carcinoma of the breast complicated by skeletal metastases. The clinical, röntgenographic and pathological study of these cases presented several points of interest in connection with the questions of prognosis and therapy of carcinoma of the breast. The following is a brief résumé of the clinical histories of the cases:

CASE I.—Mrs. B., aged thirty-nine, an advanced carcinoma of the right breast with involvement of the axillary and the supra-clavicular glands. A radical amputation of the breast was done on November 17, 1913. Pain in the hip-joints developed two months after the operation; six months after the operation the patient became bedridden, developed perfect clinical evidence of metastases in both femurs, and died nine months after the operation. No autopsy could be obtained.

CASE II.—Mrs. G., aged forty-three, was admitted to the Montefiore Hospital on December 3, 1913. Two years previous to the admission to the hospital the patient underwent a radical amputation of the right breast for carcinoma. The patient died on December 31, 1913. Autopsy showed metastases of carcinoma in the viscera and in the sternum. The latter served for pathological study.

CASE III.—Mrs. B. H., aged forty-one, admitted to the Montefiore Hospital on January 21, 1914, with an inoperable carcinoma of the right breast, painful spine and inability to walk. Clinical and Röntgen examination showed metastases in the eighth, ninth and tenth ribs, and in both femurs; the patient died on May 20, 1914. Autopsy showed carcinoma of the breast and metastases in the axillary lymph-glands, pleura, both trochanters and the

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eighth, ninth and tenth ribs. A microscopic study was done of the ribs and trochanters.

CASE IV.—Mrs. T. S., aged thirty-nine, admitted to the hospital May 14, 1914, with a recurrence of a carcinoma of the right breast which was amputated about six months previously. Clinical and röntgenographic examinations revealed metastases in the right femur. Patient died June 17, 1915. Autopsy showed medullary carcinoma of the breast, metastases in the axillary, cervical, mediastinal, bronchial and retroperitoneal lymph-glands and in the head of the right femur. The metastasis in the femur served for pathological study.

CASE V.—Miss R. S., aged forty-two. A radical amputation of the right breast was done in August, 1915, for carcinoma with involvement of axillary and supraclavicular lymph-glands. Four months later there developed a kyphosis, a swelling at the regions of both trochanters and inability to walk; two months later the patient began to complain of severe headaches, became delirious, then developed a right hemiplegia which was followed by death two days later. No autopsy could be obtained, but there was undoubted clinical evidence of metastasis in the spine.

CASE VI.—Mrs. R. E., aged fifty-six. A radical amputation of the left breast for carcinoma was done in the Brooklyn Jewish Hospital in August, 1913. Three weeks after the operation there set a pain in the right thigh, later the left thigh became involved. The patient was admitted to the Montefiore Home and Hospital on November 10, 1914. One month after admission she sustained a fracture of the right femur. The patient died on January 1, 1916. Autopsy showed metastases in the liver, ribs and both femurs. This case showed a very slow progress of the skeletal metastases; pain in the thighs developed three weeks after the operation, consequently the metastases were already present during the operation, since the cancer nodule in the bone must obtain a certain size before the pains appear and still the patient lived two and a half years after the operation.

The analysis of the röntgenograms gives very interesting indications of the pathological development of the process, the plates taken immediately after the fracture occurred show the fracture in the right femur (Fig. 1) and destruction of bone, *i.e.*, tumor masses further down the shaft (Fig. 2), and reveal nothing abnormal in the left femur (Fig. 3); röntgenograms taken ten months later show in the right femur (Fig. 4) bridges of newly-formed bone in the area of the old fracture. Indeed the latter appears to be firmly healed, a fact which was noted clinically. Below the old fracture there has taken place a new fracture. The left femur (Fig. 5) shows now distinct areas of metastases. It is

very striking that the sawed open surface of the left femur (Fig. 6) shows the metastases practically in the same positions as on the röntgenogram.

CASE VII.—Mrs. A. B., aged forty-five, previous illness began a year ago with pain in the left hand, radiating down from the shoulder. She consulted a physician who called her attention to little lumps in the left breast: she went to Mt. Sinai Hospital where her left breast was amputated; after leaving the hospital the patient experienced great pains in various regions of the body, chest, legs, back, etc. The pain grew gradually worse, until six months later she went to Gouverneur Hospital, where she stayed fourteen days. The patient became gradually weaker, paler, and complained of headaches, pains in various regions of body, loss of weight and impairment of vision. On October 1, 1915, she was admitted to the Montefiore Home and Hospital. On admission röntgenograms of nearly the whole skeleton of the patient were taken with the following results:

Hips: Marked irregular bone destruction of the upper part of both femurs and the pelvic bones (Fig. 7).

Shoulders: Advanced irregular bone absorption of all the bones entering into the formation of the shoulder-joints.

Ribs: The posterior parts of almost all the ribs, especially on the left side, show a great number of spots of bone destruction. Fig. 8 shows the condition of both shoulders and the ribs and Fig. 9 the same in radius and ulna.

Skull: All the bones of the skull show a great amount of irregular bone destruction of both tabulæ (Fig. 10).

All the abnormalities in the skeleton stated above were due to multiple metastases of carcinoma in the bones.

December 30, 1915: The palpation of the skull shows a protuberance over the left temporal region, consisting of a soft diffuse mass, about 2 inches in diameter (a massive bone metastasis).

Palpation of the left side of the chest wall is painful. Second, third and fourth ribs feel rough and nodular. The left knee-joint is swollen and painful; an enlargement is apparent at the head of the tibia.

January 13, 1916: A swelling has developed in the middle of the right clavicle, which is soft on palpation, and indicates a complete destruction of the bone in this section of the metastatic area.

January 19, 1916: Patient's speech is not clear, slow and confused; complains more of pain than heretofore, and in addition to the already found swellings, she developed a swelling over the right Poupert's ligament which is soft, doughy and easily compressible, but not tender.



FIG. 1.—Case VI. Röntgenogram of the neck of the right femur. The arrows show the line of fracture.



FIG. 2.—Case VI. Röntgenogram of the shaft of the right femur. The arrows show the metastatic tumors.



FIG. 3.—Case VI. Röntgenogram of the neck of the left femur. It shows no abnormality.



FIG. 4.—Case VI. Röntgenogram of the neck of the right femur, taken ten months later. Shows double fracture.

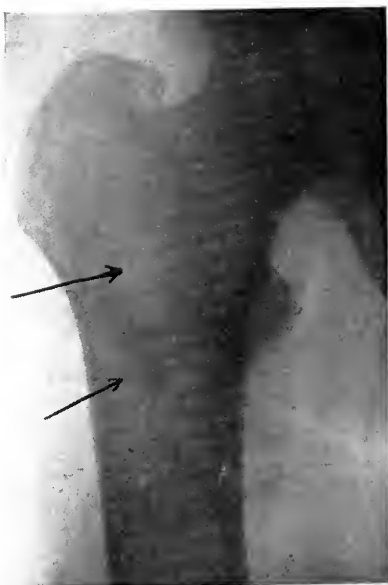


FIG. 5.—Case VI. Röntgenogram of the neck of the left femur, taken ten months later. The arrows show the light spots of bone absorption—metastases.



FIG. 6.—Case VI. Sawed open surface of the left femur. Shows metastases and hemorrhages.



FIG. 7.—Case VII. Röntgenogram of femur and pelvic bones. Shows irregular bone destruction.





FIG. 8.—Case VII. Röntgenogram of chest. Shows absorption of bone.



FIG. 9.—Case VII. Röntgenogram of humerus, radius and ulna. Shows extensive irregular bone destruction.



FIG. 10.—Case VII. Röntgenogram of skull. The arrow shows bone absorption.



FIG. 11.—Case VIII. Röntgenogram of spine. Shows absorption of bone of the eleventh and twelfth dorsal vertebrae.



FIG. 12.—Case VIII. Röntgenogram of the neck of femur. The arrow shows bone absorption in the upper portion of the neck.



FIG. 13.—Case IX. Röntgenogram of the left half of the chest. Shows destruction of bone in the left clavicle.



FIG. 14.—Case X. Röntgenogram of the spine. Shows bone destruction in the centre and new bone formation in the periphery (two bridges) in the contiguous portions of the second and third lumbar vertebrae.



FIG. 15.—Case X. Röntgenogram of the spine taken one year later. Shows some increase in the new bone formation.



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January 22, 1916: Patient was unconscious for the last two days; the patient died on January 22, 1916. An autopsy could not be obtained, but the clinical history, which was given here at greater detail than in the other cases, as well as the röntgenograms prove conclusively the presence of an extensive skeletal carcinoma. The case presents the most extensive involvement of the skeleton of any described in the literature and shows that skeletal metastases may develop below the elbow. This last fact is important since, as stated above, Handley bases his pathological conception and operative technic to a great extent on the fact that skeletal metastasis in carcinoma of the breast does not develop below the elbow or knee-joint.

CASE VIII.—Mrs. R. R., aged forty-three, admitted to the Montefiore Home and Hospital January 16, 1916. Present illness began May, 1915, when the patient noticed a very small lump, the size of an orange seed, underneath the skin of the left breast. In August the breast was amputated at Beth Israel Hospital. In October the patient began to complain of pain in lower extremities and back.

A röntgenogram taken on January 20, 1916, showed great absorption of bone of the eleventh and twelfth dorsal vertebræ (Fig. 11). The entire lumbar spine had a worm-eaten appearance: the upper portion of the neck of the right femur (Fig. 12) shows multiple areas of bone absorption. Patient died on February 13, 1916. The autopsy performed by Dr. B. S. Kline showed carcinoma of breast with recurrence in wound following removal. Metastases to the regional lymph-glands, liver, pancreas, lung, right femur and in the eleventh and twelfth dorsal vertebræ. The metastases in the bones were studied microscopically.

CASE IX.—Mrs. B., aged fifty-four. The patient underwent a radical amputation of the left breast for carcinoma in 1911. In the summer of 1914 there developed a swelling measuring 2 inches long,  $\frac{3}{4}$  inch wide, and 1 inch high, adherent to the left clavicle. The röntgenogram (Fig. 13) shows partial destruction of the bone and consequently a metastasis in the left clavicle. The case was referred to the writer (by Dr. Bodenheimer) in August, 1914. Under a combined radium and Röntgen treatment the swelling disappeared. The case was reported in September, 1915.<sup>8</sup> Now nearly two and a half years after beginning of the treatment, the patient is clinically well and does not show any recurrence of carcinoma anywhere.

CASE X.—Mrs. D. L., aged forty. The patient had a radical operation of the right breast for carcinoma done in May, 1915. On leaving the hospital the patient felt perfectly well for two

weeks, when she began to experience pain for the first time. This pain was situated in the region of the lower lumbar vertebræ, the patient claiming that the pain was similar to that felt during child-birth. The above has persisted ever since. With the onset of pain there developed loss of weight and general weakness. The pain was very severe and the patient has been confined to bed. The patient was admitted to the Montefiore Home and Hospital on November 10, 1915. A röntgenogram of the spine taken on admission (Fig. 14) showed a slight destruction of the contiguous portions of the second and third lumbar vertebræ with some bone condensation and very marked new bone formation in form of bridge formation on both sides.

The patient received Röntgen treatment both over the chest and the region of the second and third lumbar vertebræ. At present, one year after admission, the patient left the hospital greatly improved, able to walk around and work. A later röntgenogram (Fig. 15) shows apparently some increase in the bone formation in the region of the second and third vertebræ.

#### CLINICAL AND PATHOLOGICAL CONSIDERATIONS

The clinical and röntgenologic study of the cases shows that the skeletal metastases undoubtedly were present in all of them at the time of the operation. Pain in the different parts of the skeleton either appeared before or very soon after the operation. The röntgenograms taken upon the admission to the hospital showed usually an extensive involvement of the bone, and the identical condition was found at the autopsy. All this shows that the metastases were of long standing. Statistical investigations as stated above indicate that skeletal metastases of carcinoma may be very slow in their development. It may take years before clinical manifestations of any kind present themselves. The pathological studies of the writer bear out and elucidate the reasons for this phenomenon.

The metastasis of carcinoma in the bone begins its development within the marrow, and when the group of cancer cells are small, the surrounding bone-marrow appears quite normal. Figs. 16 and 17 present microphotographs of two such small cancer nodules within a bone-marrow space. Von Recklinghausen claims that the development of the metastasis is preceded by a hyperæmia and hæmostasis due to the obstruction of the capillaries by endovascular tumor emboli. In the specimens studied by the writer hemorrhages and hyperæmia were noted frequently around large tumor masses, in the femur, for instance (Fig. 6), but not around minute metastatic nodules. In

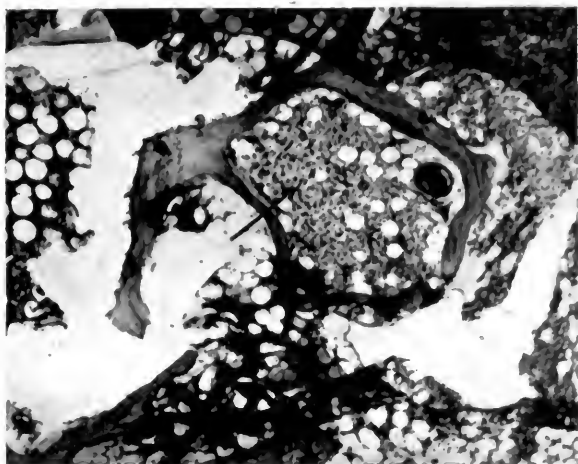


FIG. 16.—Microphotograph of a bone-marrow space. The arrow shows a small island of cancer cells. (Low magnification.)

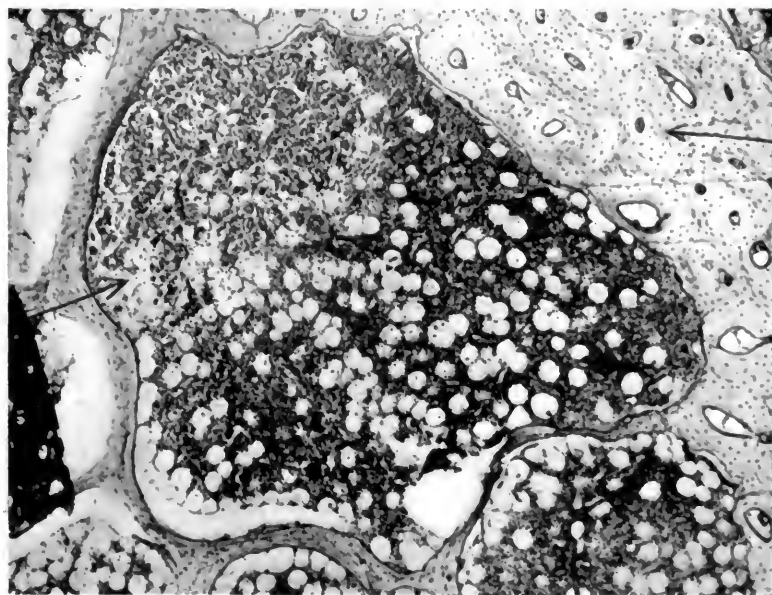


FIG. 17.—Microphotograph of a bone-marrow space with a small nodule of carcinoma (larger than in Fig. 16). The arrow *a* shows the carcinoma. The arrow *b* shows compact bone. (Low magnification.)

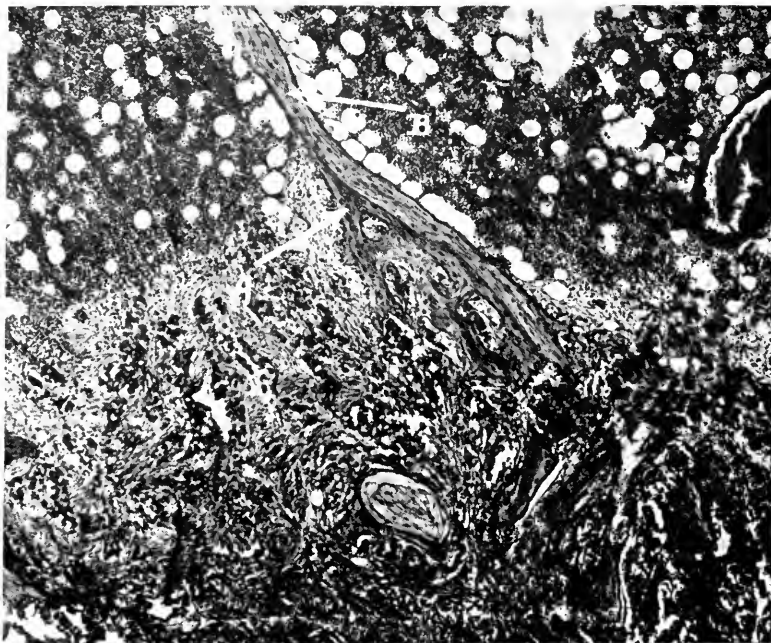


FIG. 18.—Microphotograph shows a great deal of new bone formation in the vicinity of an old bridge of compact bone tissue. *B* shows old bone; *A*, new bone.

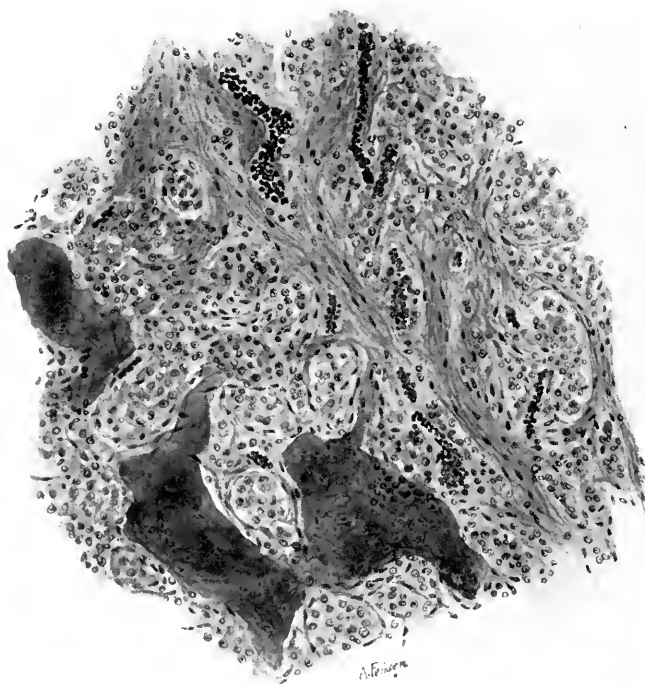


FIG. 19.—From a microscopic section of a skeletal metastasis stained with Van Gieson. Shows collagen fibrils emerging from the old bone and uniting with other fibrils.



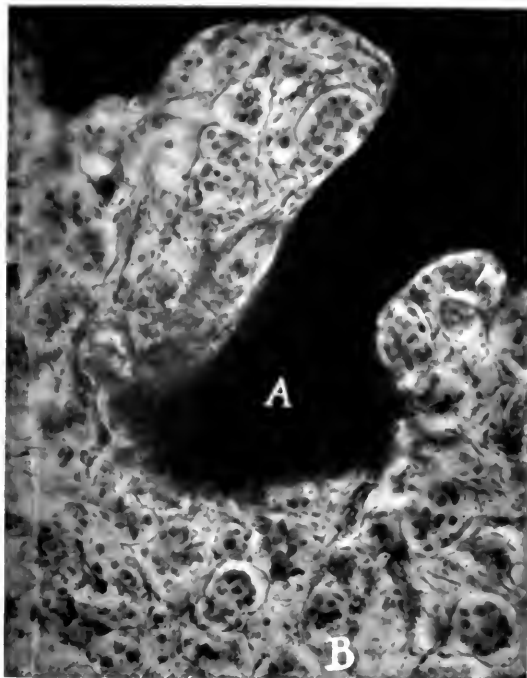


FIG. 20.—Microphotograph, two bone lacunæ filled with carcinoma cells. A, shows bone; B, carcinoma. (Low magnification.)



FIG. 21.—Röntgenogram of case of sarcoma of mandible taken before treatment. Shows tumor with two radium tubes *in situ*.



FIG. 22.—Röntgenogram of case of sarcoma of mandible taken after treatment. The arrows show the new bone formation.

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the latter instances as stated above no morphological abnormality could be found in the bone-marrow.

As the tumor nodule increases in size it approaches and invades the compact osseous tissue or the compact osseous partitions of the cancellated bone, and then there begin to appear the characteristic changes in the bone tissue. It is generally accepted that there are two classes of skeletal metastases of carcinoma: *osteoplastic*, in which there takes place a great deal of new bone formation around the metastatic tumor, and *osteomalacic*, in which the change of the normal tissue surrounding the metastasis consists in extensive destruction of the compact bone. These two distinct conditions can be easily differentiated on the gross inspection of skeletal metastases. However, the microscopic study of the cases of the present investigation by the writer has shown that both conditions are usually present side by side, and only in one case *osteosclerosis*, or new bone formation, predominates, while in another *osteoporosis*, or the destruction of the old bone, is mainly evident. Figs. 18 and 19 show an extensive new bone formation, while Fig. 19 presents only destruction of the old bone, and both specimens were obtained from different regions of the same metastatic tumor.

The mechanism of the bone destruction in metastases of carcinoma differs from the one observed in inflammatory osteoporosis. Von Recklinghausen<sup>9</sup> first made the observation that the large polynuclear osteoclasts which destroy the bone in osteoporosis are very seldom found in the lacunæ of the bone surrounding a growing metastasis of carcinoma. This fact was confirmed by most of the subsequent investigators. In view of the absence of the large osteoclasts, Von Recklinghausen presumed that there takes place in the bone a softening by the removal of the inorganic salts, and a subsequent absorption without the aid of any cells, a condition similar to the one found in osteomalacia. Apolant,<sup>10</sup> Erbslöh,<sup>11</sup> Askanazy,<sup>12</sup> are also of the opinion that osteoporosis in skeletal carcinoma may take place without the aid of special cells. On the other hand, Wolff<sup>13</sup> and Goetsch<sup>14</sup> believe the cancer cells act as osteoclasts and destroy the compact bone, and Axhausen<sup>15</sup> maintains that the small elongated mononuclear connective-tissue cells, frequently found close to the walls of the lacunæ, are special osteoclasts derived from the cancer stroma. In the specimens studied by the writer both carcinoma cells, as well as the small connective-tissue stroma cells, are found in close immediate apposition to the walls of the lacunæ. The carcinoma cells were so frequently the only cellular elements within the lacunæ of the bone that there

cannot be any doubt that carcinoma cells act as direct osteoclasts. Fig. 20 shows lacunæ filled with carcinoma cells. The impression gained by the writer is that the small stroma cells only subsequently enter between the bone and the carcinoma cells. But even if the possibility be admitted that occasionally the stroma cells may act as osteoclasts, it seems quite apparent that the tumor itself, by the aid of its formed elements, first destroys the bone and then grows by occupying the produced space.

While the mechanism of osteoporosis in skeletal metastasis as stated above is at least similar to the mechanism of the destruction of any normal tissue surrounding a growing malignant tumor, the osteosclerosis, or the extensive formation of new bone tissue, is characteristic of skeletal metastases.

Von Recklinghausen claims that this extensive new bone formation is due to the hyperæmia described by him and mentioned above. Courvoisier<sup>16</sup> and Kaufman<sup>7</sup> maintain that a metastasis in the bone is always surrounded by a zone of inflammation, and this latter caused the osteosclerosis. Askanazy<sup>12</sup> thinks that the metastasis at first produces an osteoporosis, which is followed by a bone necrosis, and the necrotic bone acting as a foreign body caused a new bone formation. Wolf,<sup>13</sup> Courvoisier,<sup>16</sup> and Kaufman,<sup>7</sup> are of the opinion that carcinoma cells may act as osteoclasts and form new bone tissue. Fig. 19 presents a picture very frequently observed by the writer. It shows collagen fibrils developing in abundance from the old bone. These fibrils gradually unite in thick bundles and subsequently form new bone tissue. The latter is clearly formed from the constituent parts of the old bone tissue. On the other hand, as stated above, the writer did not observe any hyperæmia, inflammation or any other abnormality of the bone-marrow at the beginning of the development of the metastases. Neither did the writer find any necrosis of the bone in any of the specimens examined. It must be concluded in agreement with Axhausen's<sup>15</sup> conception that some unknown chemical irritant emanating from the carcinoma cells acts on the old bone tissue and stimulates its proliferation.

Thus there constantly and side by side take place in skeletal metastasis two processes. On one hand the tumor cells destroy the normal bone tissue and occupy its place, and on the other hand the remaining bone tissue proliferates and creates new bone. The latter is quite probably an attempt at self-defense on the part of the organism. The newly-formed bone tissue may compress and destroy the cancer cells, or at least inhibit their proliferation. Case VI shows such a condition. There took place a pathological fracture in the right femur, which

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subsequently became firm and seemed clinically healed (Fig. 4), while later a second fracture took place below the first. Here apparently nature succeeded in healing one metastatic focus in the bone, while in another place the tumor grew unchecked. Such temporary healing of a pathological fracture within a skeletal metastasis was described in several instances.

Thus the microscopic study of skeletal metastasis gives a clear evidence of the interaction which always takes place between the normal organ tissue and the cancer cells in the beginning of the development of a metastatic tumor from a transported cancer embolus. Upon the result of such an interaction depends the success or failure of the formation of metastasis. In the bone the conditions are evidently more favorable for at least temporary suppression of the proliferation of the cancer cells by the newly-forming bone tissue, and therefore skeletal metastases develop only slowly and appear late.

### THE PROGNOSTIC SIGNIFICANCE OF SKELETAL METASTASES

The radical operation for a malignant tumor means a complete eradication of all tumor tissue from the organism. It is patent that a radical operation in this sense of the word is impossible as long as a skeletal metastasis was diagnosed before the operation. Furthermore, Heurtaux has shown that ten years after a breast amputation only 12.32 per cent. remain free of the disease and twenty years after the operation only 2.46 per cent. remain free. It would then seem that in the overwhelming majority of all the cases of carcinoma of the breast the best surgical methods of treatment do not completely eradicate the disease, but only prolong life. But on the basis of the latter interpretation of the therapeutic results in carcinoma of the breast skeletal metastases give a better prognosis than metastasis in other organs, since they are much slower in their development and may therefore be more readily controlled.

### RADIUM AND RÖNTGENOTHERAPY OF SKELETAL METASTASES

As stated above, the radical amputation of the breast in the presence of skeletal metastases cannot cure completely the disease. On the other hand, the operation if correctly performed may prolong the life of the patient, since the removal of the primary tumor diminishes the possibility of subsequent formation of metastases in other organs than the bone. But the operation, while aiming at a complete as possible removal of the main mass of the tumor, does not need to be entirely radical. It is more important not to handle and massage the tumor too energetically during the operation and thereby transport cancer cells

into the circulation, than to remove every vestige of it. The writer<sup>8</sup> has shown in a previous publication that small islands of tumor cells can be destroyed by radium and Röntgen rays, even at a great distance from the skin, and it should therefore be easy to eradicate by the aid of the radiations small remnants of the tumor located in the axilla, or over the chest wall. The diathermic coagulation of tissue which the writer<sup>17</sup> discussed in previous publications, and which destroys the carcinoma cells *in situ* without opening the blood and lymph channels, may become the operative methods of choice for such incomplete operations when the correct technic is developed.

Thus the correct treatment of carcinoma of the breast, complicated with skeletal metastases, consists in the operative removal of the gross tumor mass, combined with radium and Röntgen therapy. The radiations in a postoperative case of carcinoma of the breast should not be given only over the operative field and over the chest wall, which is the procedure generally adopted to-day, but should include, if not the whole skeleton, at least the spine and the heads of both femurs. Moreover, this combination of surgery and radiotherapy should be the method of choice in all advanced cases of carcinoma of the breast, even when there is as yet no evidence of skeletal metastases.

The writer has shown<sup>18</sup> that one of the important effects of radium and röntgenotherapy consists in the formation of an extensive connective-tissue stroma, surrounding and compressing the tumor cells. In skeletal metastases this stroma, as the pathological study reported above shows, is transformed into bone. It is thus self-evident *a priori* that the radiotherapy must enhance the results of the attempts at cure produced by nature.

In a case reported by the writer in 1915, though not a metastatic carcinoma, but a primary sarcoma of the bone (right mandible), new bone formed under the influence of radium and Röntgen therapy. Eight weeks after the beginning of the treatment, the tumor had completely disappeared, and instead there was present a large cavity lined by a shell of bone. Fig. 20 shows a röntgenogram taken immediately at the beginning of the treatment, with the radium tubes *in situ*. There is seen a nearly complete loss of bone around the tumor. Fig. 21, a röntgenogram taken after treatment, shows that the swelling is surrounded by a great deal of new-bone formation. The Cases IX and X of the present report clearly show that radium and röntgenotherapy may cure clinically skeletal metastases of carcinoma. Case IX is clinically well and shows no recurrence in other regions of the body for two and a half years.

## SKELETAL METASTASES IN CARCINOMA OF THE BREAST

Case X is now clinically well one year after admission to the hospital, while a year ago it presented the picture of a most hopeless condition, ever met even among cases of inoperable carcinoma. Though it cannot be stated as yet for how long the patient's life will be prolonged, the achievement in this case is certainly sufficient to encourage further attempts at the same method of treatment.

It would lead too far to go here into details of the technic of radiotherapy, but one point must be considered, the treatment must be continued at stated intervals for a long time, and if it is interrupted too soon, the metastatic tumor may become active again, destroy a large area of bone and then the subsequent radiations will be of no avail.

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## METASTASIS OF CANCER IN THE CENTRAL NERVOUS SYSTEM\*

AN EXPERIMENTAL AND CLINICAL STUDY

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Metastasis of carcinoma or sarcoma in the brain is a comparatively rare anatomic finding. Krasting (1) made an exhaustive statistical study on the subject, based on an analysis of 12,730 autopsies performed in the Basel Hospital between the years 1870 to 1905. 1,078 cases of carcinoma were found among these autopsies. The brain was examined in 817 cases, in 39 of which metastasis of carcinoma was found. There were 160 cases of sarcoma, and of 118 cases in which the brain was examined, metastasis was found in 14. Thus metastases of carcinoma were found in 4.7 per cent. of the cases examined, and in 11.6 per cent. of sarcoma. R. Williams (2) as a result of an analysis of 893 autopsies of carcinoma of the breast, found metastasis in the brain in only 6.6 per cent. of the cases. These figures present a very small percentage, when we consider that more than half of all cases of cancer show metastasis in various organs.

Krasting and Silvan (26) found that metastases are more fre-

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quently met with on the left side of the brain than on the right, but Offergeld (27) denies this.

Another characteristic feature of metastasis of the brain is the varying frequency of its occurrence depending upon the seat of the primary tumor. In Krasting's material metastasis in the central nervous system was found in 18.8 per cent. of cases of carcinoma of the breast, in 22.2 per cent. of cases of carcinoma of the prostate, and in only 3.4 per cent. of cases of carcinoma of the uterus. Not a single metastasis in the central nervous system was found in 227 cases of carcinoma of the stomach.

These striking peculiarities in the occurrence of metastasis of carcinoma in the central nervous system must be due to certain phenomena in the general mechanism of metastasis formation. A brief consideration of the theoretical conceptions in connection with this mechanism is therefore indispensable for a clearer understanding of the subject matter of this investigation.

The opinion prevails among pathologists that the differences in the frequency and the localization of metastatic tumors is due to the greater or lesser facility with which cancer cells reach a certain locality.

The only conceivable mode of formation of metastasis is the proliferation of a group of cancer cells, which have been transported through the blood and lymph channels to distant parts or organs of the body. These particles of cancer tissue act as emboli and, finding lodgment in some region of the organism, form secondary metastatic tumors.

Handley (3) attempted to prove recently that embolism has no significance in the formation of metastasis of carcinoma of the breast. According to his conception, metastasis is formed by a process of "lymphatic permeation." The tumor cells grow along the lymphatic vessels until they reach the nearest lymph glands, and from these glands the cells enter the next lymphatic vessel. This process is continuous, and the appearance of an apparently isolated tumor nodule is due to the fact that a perilymphatic fibrosis destroys the permeated lymphatic vessels which form the lines of communication. The formation of metastases in distant organs Handley ascribes to the proliferation of cancer cells which escape from the subserous lymphatic plexuses into the serous cavities, pleura, or peritoneum. The cells are then distributed through these cavities under the influence of gravity and of visceral movements, and implanted on the serous surface of the viscera.

Handley's theory is inadequate to explain all the phenomena of

formation of metastasis even in cancer of the breast. Only the conception of embolic transportation of tumor cells accords with the main factors of the process of formation of metastases.

Until recently it was generally accepted that carcinoma metastasises through the lymphatics exclusively and that only sarcoma metastasises through the blood-vessels. von Recklinghausen (4) was the first to indicate that carcinoma may also metastasise through the blood-vessels. The most thorough study, however, of the subject of the relation of blood-vessels to the formation of metastasis in carcinoma was made by Goldmann (5) and by Schmidt (6). Goldmann proved that there is an extensive invasion by tumor cells of the coats of blood-vessels in carcinoma as well as in sarcoma. The paths of entrance of the cancer cells into the vascular coats appear to be the vasa vasorum, since the blood-vessel walls do not contain any lymphatics. This supposition is in accord with the fact that in arteries, the tumor cells rarely proceed further than the outer coat, whereas in veins they are generally found beneath the intima. The same difference takes place in the distribution of the nutrient vessels in the arteries and veins. While in the former the vasa vasorum usually remain within the limit of the outer coat, they extend in the veins beyond the middle coat into the region of the intima. The same investigator has shown, further, that fluid injected into the jugular vein passes with the greatest ease from the vein into the adjacent lymph glands. The conclusion must be drawn from Goldmann's investigations that there is a very intimate relation between the lymph- and blood-vessels, and that carcinoma cells enter blood-vessels just as readily as do sarcoma cells. Indeed, a tumor cell may penetrate a vein with greater ease than a large lymphatic vessel, since in the latter the vasa vasorum do not penetrate as near the inner coat as they do in the vein.

Schmidt examined forty-one cases of carcinoma of the abdominal viscera, selected at random from his autopsy material, for possible metastases in the lungs. In fifteen cases he found, on microscopic examination, small nodules either surrounded by a stroma of connective tissue formed apparently by the endothelium of the blood-vessel, or else consisting of a free group of cancer cells which seemed to have been transported more recently. The coats of the small pulmonary arteries, in which the cancer nodules were usually found, showed no lesion. The tumor cells apparently did not break through the wall of the blood-vessel from a focus of local dissemination, but were transported from the primary tumor or from a distant metastasis. Schmidt inclines to the opinion that

the carcinoma cells found in the lungs were transported through the lymphatic vessels, thoracic duct, subclavian vein, and pulmonary circulation. He finds support for this supposition in the fact that in three cases where nodules were found in the lungs there were visible metastases only in the regional lymph glands. Furthermore, he actually found small carcinoma nodules within the lumen of the thoracic duct. He does not exclude, however, the possibility that in certain cases, in accordance with Goldmann's findings, the cancer cells may have entered a minute blood-vessel either within the primary tumor or within the metastatic tumor of the regional lymph gland, and in this way have reached the pulmonary vessel. Schmidt arrived at the conclusion that in carcinoma of abdominal organs, cancerous embolism of the small arteries of the lungs occurs with great frequency. Only a small proportion of these emboli give rise to metastatic tumors, because most of them are encapsulated and rendered harmless. A certain number of these emboli may, however, pass the pulmonary circulation and form metastases in distant organs. All these investigations seem to have established firmly the fact that cells of all malignant tumors may be transported either through the lymphatics or the blood-vessels.

In view of this conclusion, nearly the same facility exists for the transportation of tumor emboli from any primary tumor into distant parts of the organism.

The difference in the channels of transportation alone is thus inadequate to explain the variations in the frequency and the localization of the metastatic tumors. Numerous additional theories are offered in explanation of the phenomena; von Recklinghausen, for instance, believes that the formation of bone metastases in carcinoma is due to the fact that the veins and capillaries of the bone marrow have thin walls and are not collapsible. These morphological peculiarities favor the accumulation of carcinoma cells within these blood-vessels. Lubarsch (7) is of the opinion that the relative sizes of the cancer cells and of the minute blood vessels of an organ are of importance for the formation of metastases.

On the other hand, Neusser (8), and Bamberger and Paltauf (9) believe that certain organs possess a peculiar affinity for the cells of certain types of malignant tumors. This selective affinity may be due to some peculiarity in the chemical constitution of the organ. More recently Albrecht (10) and Ehrlich (11) advanced the hypothesis that the development of a metastatic tumor is determined by the chemical metabolic condition of the entire organism. Their idea is that the growth of a secondary tumor depends upon

the character of the primary growth. If the latter is very malignant and reaches a large size, then it uses up all the specific food required by the multiplying cancer cells, and none remains for the cells of the secondary growth. On the other hand, when the primary tumor is growing slowly, a sufficient amount of the specific food is left for the development of the metastatic tumor.

There is the same difference of opinion concerning the mechanism of formation of metastases in the central nervous system. Siefert (12) lays stress mainly on the transport through the blood-vessels, Knierim (13) and Curschman (14) consider the lymphatics and the subarachnoid spaces the channels of transport. On the other hand Cruveilhier (15) claims that the central nervous system offers a greater resistance to the growth of cancer than do other organs. O. Fischer (16) states even that grey matter offers greater resistance to the formation of metastases than does white matter.

#### THE BEHAVIOR OF A SARCOMA OF THE FOWL WHEN INOCULATED IN ORGANS

The correct estimation of all the complex phenomena involved in the mechanism of formation of metastases is extremely difficult.

Experimental cancer research on inoculable malignant tumors of lower animals offers the opportunity of studying the subject under less complicated conditions than is obtained in human pathology. Particles of the tumor may be introduced into various normal organs of normal animals and the subsequent changes of the tumor as well as of the organ, the soil so to speak of inoculation, may be observed.

The first spindle cell sarcoma of the fowl described by Peyton Rous (17), when inoculated into the breast muscle of a chicken, is extremely malignant in the new host. The tumor infiltrates and destroys the surrounding tissues and organs; undergoes extensive local dissemination and metastasizes in the internal organs. The inoculated animal soon emaciates and dies, usually within three weeks after the inoculation. This tumor is biologically analogous in many respects to human sarcoma and seems to be well adapted for an experimental study of the mechanism of metastasis formation.

The experiments consisted in the inoculation of the tumor in different organs, and in a comparative study of the biological characteristics of the tumors developed in the new host and of the behavior of the latter.

The biological phenomena considered in the present investigation were the clinical malignancy, as manifested by the length of

life of the inoculated animal, the size of the primary growth, and the frequency and location of metastases. The tumors were inoculated in the liver, in the gizzard, and the brain. For each operated animal a control animal was inoculated in the right pectoral muscle, with the same quantity of tumor obtained from the same source. All the animals were allowed to die; and after death autopsies were performed and all the internal organs examined for metastases visible on gross inspection. Every suspicious area and nodule observed on the surface of an organ or on the cut surface was examined microscopically. The extent of local invasion and destruction of the organ caused by the growth of the tumors was also determined by microscopical examination.

CHART I  
INOCULATION INTO LIVER

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	13	<i>E</i>	*	*	—	—	—	—	—	—
2	11	"	—	—	—	—	—	—	—	—
3	14	<i>L</i>	—	—	—	—	—	—	—	—
4	23	<i>E</i>	*	—	—	*	—	—	—	—
5	19	"	—	—	—	—	—	—	—	—
6	12	"	*	—	*	—	—	—	—	—
7	16	"	—	—	—	—	—	—	—	—
8	14	"	*	—	—	—	—	—	—	—
9	17	"	*	—	—	*	—	—	—	—
10	20	"	—	—	—	—	—	—	—	—
11	31	"	—	—	—	—	—	—	—	—
12	17	"	—	—	—	—	—	—	—	—
13	18	"	—	—	—	—	—	—	—	—
14	14	<i>S</i>	*	—	—	—	—	—	—	—
15	13	<i>E</i>	*	—	—	—	—	—	—	—
16	13	"	—	—	—	*	—	—	—	—
17	13	<i>L</i>	*	—	—	—	—	—	—	—
18	18	<i>E</i>	*	—	—	—	—	—	—	—
19	17	"	—	—	—	*	—	—	—	—
20	16	"	—	—	—	—	—	—	—	—
21	23	"	*	—	—	—	—	—	—	—
22	19	<i>M</i>	*	—	*	—	—	—	—	—
23	15	<i>L</i>	*	*	—	*	—	—	—	—
24	22	<i>E</i>	—	—	—	—	—	—	—	—
25	12	<i>L</i>	*	—	—	—	—	—	—	—
26	16	"	*	—	—	—	—	—	—	—
27	17	"	—	—	—	—	—	—	—	—
28	17	"	*	—	—	—	—	—	—	—
29	16	<i>E</i>	*	—	—	*	—	—	—	—

#### EXPLANATION OF CHARTS

*E* on the charts indicates a tumor which infiltrates nearly the whole breast muscle or organ. *L* indicates a large tumor, the cut surface of which is not less than 10 cm. square. *M* indicates a medium-sized tumor, of which the cut surface is not less than 5 cm. nor more than 10 cm. square. *S* indicates a small-sized tumor, of which the cut surface is less than 5 cm. square. \* indicates the presence of metastasis in an organ. — indicates the absence of metastasis in an organ. The other words and figures on the charts are self-explanatory.

## INOCULATIONS IN THE LIVER

The tumor was inoculated through an abdominal incision into the liver of 31 chickens; two died of an intercurrent disease. In 29 animals death was caused by the growth of the tumor. Of the 31 control animals in which the tumor was inoculated into the right pectoral muscle, in 26 death was caused by the growth of the tumor. Charts I and II show the comparative size of the primary tumor,

## CHART II

## CONTROLS TO INOCULATIONS INTO LIVER

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intes-tine	Pan-creas
1	17	E	—	—	*	—	—	—	—	—
2	30	"	*	—	*	—	—	—	—	—
3	13	L	—	—	—	—	—	—	—	—
4	16	S	—	—	*	—	—	—	—	—
5	16	L	—	—	—	—	—	—	—	—
6	28	E	*	—	*	—	—	—	—	—
7	26	"	*	—	—	—	—	—	—	—
8	19	"	*	—	*	—	—	—	—	—
9	14	M	—	—	—	—	—	—	—	—
10	27	E	*	—	—	—	—	—	—	—
11	39	"	*	—	*	—	—	—	—	—
12	22	"	*	—	—	*	—	—	—	—
13	21	"	*	—	—	—	—	—	—	—
14	19	"	*	—	—	—	—	—	—	—
15	25	L	—	—	—	—	—	—	—	—
16	26	E	*	*	—	—	—	—	—	—
17	23	"	*	*	—	—	—	—	*	—
18	18	M	—	—	—	—	—	—	—	—
19	21	E	*	—	—	—	—	—	—	—
20	19	M	*	—	—	—	—	—	—	—
21	29	L	*	—	*	—	—	—	—	—
22	27	E	*	*	*	—	—	*	—	—
23	23	L	*	*	—	—	—	—	—	—
24	29	E	*	—	—	—	—	—	—	—
25	18	M	*	—	*	—	—	—	—	—
26	20	E	*	*	*	—	—	—	—	—

the duration of life, the absence or presence, and the location of metastases in the operated and control animals.

The sarcoma of the fowl when inoculated into the breast muscle or into an organ grows diffusely, and it is difficult to make an accurate measurement of the tumor. Only an approximate estimation of the size of the tumor is given in the present investigation. A tumor which infiltrates nearly the whole breast muscle or organ is indicated by a letter E (*i. e.*, the *entire* breast or organ). When a cut surface shows not less than 10 cm. and not more than 15 cm.

square it is indicated by a letter L (large). When the surface is not less than 5 cm. nor more than 10 cm. square it is indicated by a letter M (medium), and when the surface is less than 5 cm. square it is indicated by a letter S (small). The average duration of life was calculated by dividing the aggregate number of days of life by the number of animals.

CHART III  
INOCULATION INTO GIZZARD

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	14	E	—	—	*	—	—	—	—	—
2	21	L	*	—	*	—	—	—	—	—
3	17	"	*	—	*	—	—	—	—	*
4	23	"	*	—	*	—	—	—	—	—
5	10	S	—	—	—	—	—	—	—	—
6	10	"	—	—	—	—	—	—	—	—
7	18	L	*	—	—	—	—	—	—	—
8	16	M	*	—	*	—	—	—	—	—
9	14	E	—	—	*	—	—	—	—	—
10	12	M	—	—	—	—	—	—	—	—
11	20	L	—	—	—	—	—	—	—	—
12	19	"	—	—	—	—	—	—	—	—
13	18	E	—	—	*	—	—	—	—	—
14	11	S	—	—	*	—	—	—	—	—
15	15	L	*	—	*	—	—	—	—	—
16	14	"	—	—	—	—	—	—	—	—
17	12	"	—	—	*	—	—	—	—	—
18	20	"	*	—	—	—	—	—	—	—
19	23	E	*	—	—	—	—	—	—	—
20	14	"	—	—	*	—	—	—	—	—
21	13	L	—	—	—	—	—	—	—	—
22	18	"	—	—	—	—	—	—	—	—
23	15	E	—	—	*	—	—	—	—	—
24	20	L	*	—	*	—	—	—	—	—
25	17	"	*	—	—	—	—	—	—	—
26	17	"	*	—	*	—	—	—	—	—
27	20	"	*	—	—	—	—	—	—	—
28	15	E	*	—	*	*	—	—	—	—

The animals inoculated in the liver presented an average duration of life of 17 days, and the controls of 22.5 days. There did not seem to be any great difference in the frequency or in the location of the metastases. The autopsies of the animals inoculated in the liver showed that the tumor had invaded (Fig. 1), and frequently completely replaced, the right lobe, in which the inoculation took place. The invasion also frequently reached the left lobe. Occasionally the tumor became disseminated throughout the peritoneal cavity and infiltrated other organs.



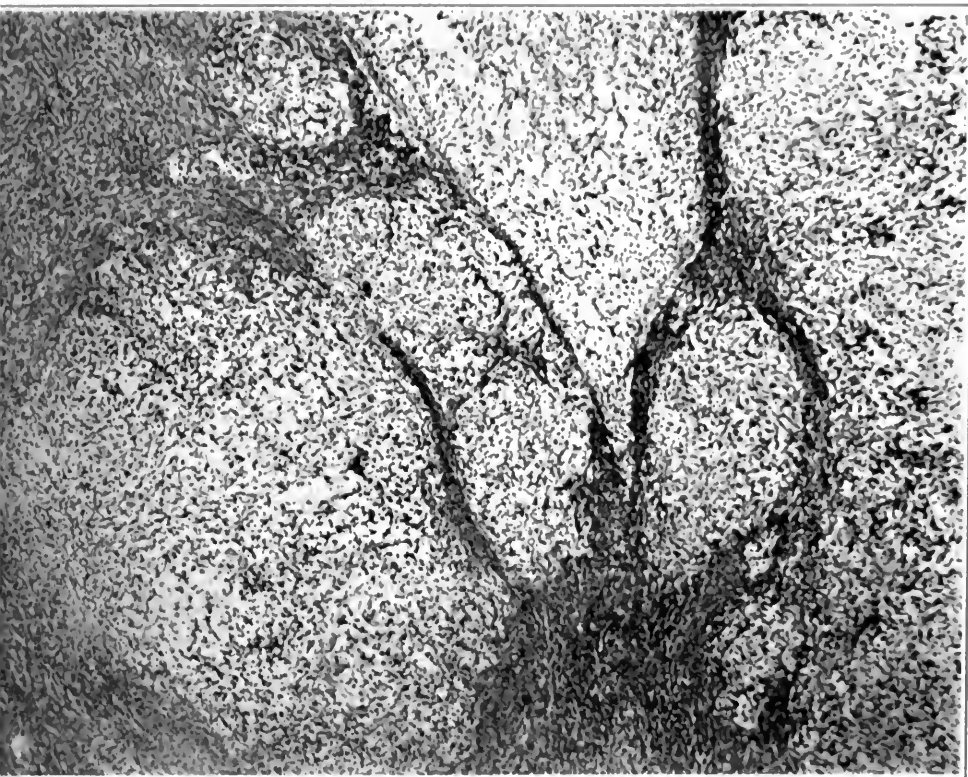


FIG. 1. Growth of sarcoma in liver. Microphotograph, low power.

#### INOCULATION IN THE GIZZARD

The tumor was inoculated through an abdominal incision in the gizzard of 31 chickens; three died of an intercurrent disease. In 28 animals death was caused by the growth of the tumor. Of the control animals in 26 death was caused by the growth of the tumor. Charts III and IV show the duration of life of the animals, the size of the primary growth and the location of the metastases, in the operated and in the control animals. The average length of life of the operated animals was 16.3 days, and of the controls 21.8 days. The animals of this group and their controls did not show any perceptible difference in either the frequency or the location of the metastases. Autopsies upon the operated animals showed that the tumor invaded and replaced the musculature of the gizzard. The dissemination of the tumor into the peritoneal cavity was even more frequent and more extensive than after inoculation into the liver.

square it is indicated by a letter L (large). When the surface is not less than 5 cm. nor more than 10 cm. square it is indicated by a letter M (medium), and when the surface is less than 5 cm. square it is indicated by a letter S (small). The average duration of life was calculated by dividing the aggregate number of days of life by the number of animals.

CHART III  
INOCULATION INTO GIZZARD

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	14	E	—	—	*	—	—	—	—	—
2	21	L	*	—	*	—	—	—	—	—
3	17	"	*	—	*	—	—	—	—	*
4	23	"	*	—	*	—	—	—	—	—
5	10	S	—	—	—	—	—	—	—	—
6	10	"	—	—	—	—	—	—	—	—
7	18	L	*	—	—	—	—	—	—	—
8	16	M	*	—	*	—	—	—	—	—
9	14	E	—	—	*	—	—	—	—	—
10	12	M	—	—	—	—	—	—	—	—
11	20	L	—	—	—	—	—	—	—	—
12	19	"	—	—	—	—	—	—	—	—
13	18	E	—	—	*	—	—	—	—	—
14	11	S	—	—	*	—	—	—	—	—
15	15	L	*	—	*	—	—	—	—	—
16	14	"	—	—	—	—	—	—	—	—
17	12	"	—	—	*	—	—	—	—	—
18	20	"	*	—	—	—	—	—	—	—
19	23	E	*	—	—	—	—	—	—	—
20	14	"	—	—	*	—	—	—	—	—
21	13	L	—	—	—	—	—	—	—	—
22	18	"	—	—	—	—	—	—	—	—
23	15	E	—	—	*	—	—	—	—	—
24	20	L	*	—	*	—	—	—	—	—
25	17	"	*	—	—	—	—	—	—	—
26	17	"	*	—	*	—	—	—	—	—
27	20	"	*	—	—	—	—	—	—	—
28	15	E	*	—	*	*	—	—	—	—

The animals inoculated in the liver presented an average duration of life of 17 days, and the controls of 22.5 days. There did not seem to be any great difference in the frequency or in the location of the metastases. The autopsies of the animals inoculated in the liver showed that the tumor had invaded (Fig. 1), and frequently completely replaced, the right lobe, in which the inoculation took place. The invasion also frequently reached the left lobe. Occasionally the tumor became disseminated throughout the peritoneal cavity and infiltrated other organs.



FIG. 1. Growth of sarcoma in liver. Microphotograph, low power.

#### INOCULATION IN THE GIZZARD

The tumor was inoculated through an abdominal incision in the gizzard of 31 chickens; three died of an intercurrent disease. In 28 animals death was caused by the growth of the tumor. Of the control animals in 26 death was caused by the growth of the tumor. Charts III and IV show the duration of life of the animals, the size of the primary growth and the location of the metastases, in the operated and in the control animals. The average length of life of the operated animals was 16.3 days, and of the controls 21.8 days. The animals of this group and their controls did not show any perceptible difference in either the frequency or the location of the metastases. Autopsies upon the operated animals showed that the tumor invaded and replaced the musculature of the gizzard. The dissemination of the tumor into the peritoneal cavity was even more frequent and more extensive than after inoculation into the liver.

CHART IV  
CONTROLS TO INOCULATIONS INTO GIZZARD

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	21	<i>E</i>	—	—	—	—	—	—	—	—
2	22	"	—	—	—	—	—	—	—	—
3	36	"	*	*	—	*	—	—	—	—
4	29	"	*	—	—	—	—	—	—	—
5	18	"	—	—	—	—	—	—	—	—
6	27	"	—	—	—	—	—	—	—	—
7	16	"	—	—	—	—	—	—	—	—
8	46	"	*	—	—	—	—	*	—	—
9	22	"	*	—	—	—	—	—	—	—
10	19	<i>L</i>	*	—	—	—	—	—	—	—
11	23	<i>E</i>	*	—	*	—	—	—	—	—
12	22	"	*	—	*	—	—	—	—	—
13	13	<i>L</i>	—	—	—	—	—	—	—	—
14	25	<i>E</i>	*	—	*	—	—	—	—	—
15	21	"	*	—	—	—	—	—	—	—
16	12	<i>L</i>	—	—	—	—	—	—	—	—
17	16	"	*	*	—	—	—	—	—	—
18	24	<i>E</i>	*	*	*	—	—	—	—	—
19	19	"	*	—	—	—	—	—	—	—
20	17	"	*	—	—	—	—	—	—	—
21	19	"	*	*	—	—	—	—	—	—
22	22	"	*	*	*	—	—	*	—	—
23	15	<i>M</i>	—	—	—	—	—	—	—	—
24	16	"	—	—	—	—	—	—	—	—
25	20	<i>E</i>	*	—	—	—	—	—	—	—
26	27	"	*	*	—	—	—	—	—	—

It was interesting to note that with one exception, none of the tumors, even those that destroyed nearly the entire musculature of the organ, invaded the mucous membrane (Fig. 2).

#### INOCULATIONS IN THE BRAIN

The inoculations in the brain were done in the following way. An opening sufficient to admit a trocar needle was made in the skull over the area of the left hemisphere. The needle was then inserted into the hemisphere to the depth of about 0.5 cm. from the surface of the skull. The opening of the skull was sealed with wax and the skin closed with a silk suture. Generally the animals stood the operation well. A certain number of them developed motor paralysis but the majority died under conditions of general depression. 34 animals were operated upon, and of these 6 died of intercurrent conditions. In 28 animals death was due to the intracranial growth of the tumors. Of the control animals, in 29 death was caused by the growth of the tumor. Charts V and VI show the duration of life of the animals, the comparative size of the primary tumors, and

the frequency and location of the metastases. The average length of life of the animals inoculated in the brain was 11 days, and of the controls 25.5 days. The size of the primary tumors and the frequency and location of the metastases of the control animals, were similar to these conditions in the other controls. On the other hand, not a single operated animal of this group showed metastases anywhere. Autopsies of the animals showed that the tumors invaded and replaced the brain tissue (Fig. 3). The size of the tumors was

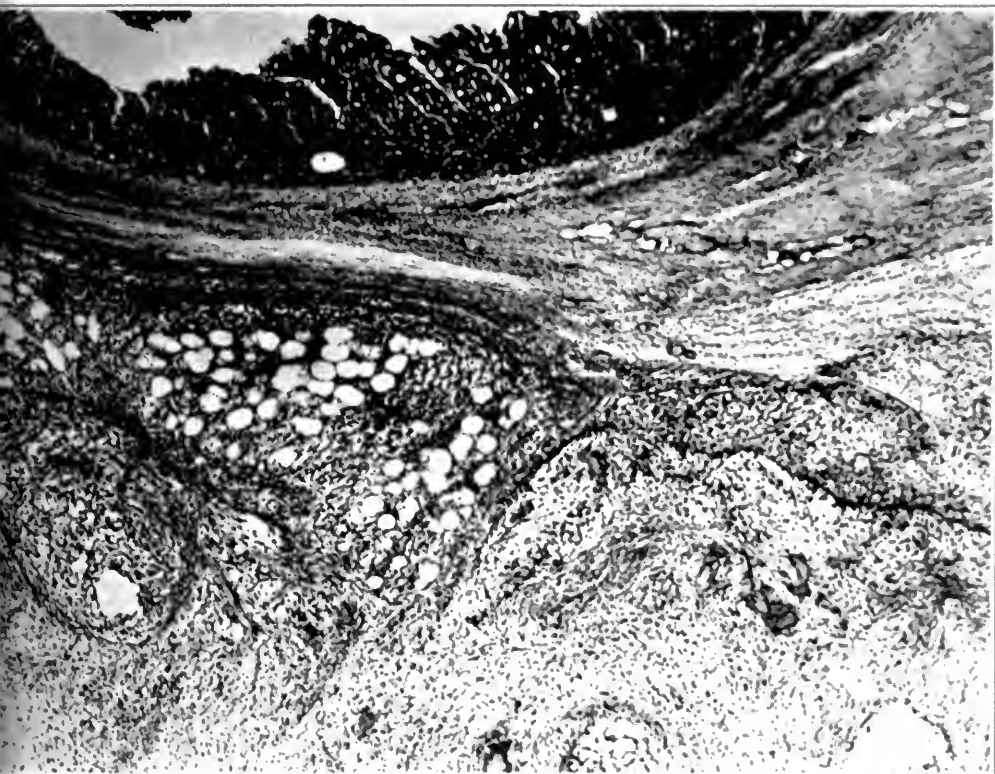


FIG. 2. Growth of sarcoma in gizzard, the mucous membrane is not invaded. Microphotograph, low power.

smaller than those which developed in an equal length of time after inoculation in the other regions cited.

#### INOCULATIONS IN THE BRAIN. SECOND SERIES

In view of the striking difference between the results of the inoculations into the brain and into other sites, it seemed advisable

to repeat the inoculations into the brain. 25 animals were inoculated and of these 14 died of intercurrent conditions. In 11 animals death was caused by the intracranial growth of the tumor. Chart VII shows the duration of life of the animals, the comparative size

CHART V  
INOCULATION INTO BRAIN. FIRST SERIES

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	9	S	—	—	—	—	—	—	—	—
2	11	"	—	—	—	—	—	—	—	—
3	11	"	—	—	—	—	—	—	—	—
4	9	"	—	—	—	—	—	—	—	—
5	9	"	—	—	—	—	—	—	—	—
6	8	"	—	—	—	—	—	—	—	—
7	13	"	—	—	—	—	—	—	—	—
8	12	"	—	—	—	—	—	—	—	—
9	8	"	—	—	—	—	—	—	—	—
10	13	"	—	—	—	—	—	—	—	—
11	6	"	—	—	—	—	—	—	—	—
12	13	"	—	—	—	—	—	—	—	—
13	14	"	—	—	—	—	—	—	—	—
14	13	"	—	—	—	—	—	—	—	—
15	9	"	—	—	—	—	—	—	—	—
16	12	"	—	—	—	—	—	—	—	—
17	14	"	—	—	—	—	—	—	—	—
18	11	"	—	—	—	—	—	—	—	—
19	9	"	—	—	—	—	—	—	—	—
20	7	"	—	—	—	—	—	—	—	—
21	15	"	—	—	—	—	—	—	—	—
22	10	"	—	—	—	—	—	—	—	—
23	19	"	—	—	—	—	—	—	—	—
24	10	"	—	—	—	—	—	—	—	—
25	11	"	—	—	—	—	—	—	—	—
26	5	"	—	—	—	—	—	—	—	—
27	10	"	—	—	—	—	—	—	—	—
28	11	"	—	—	—	—	—	—	—	—

of the primary tumors, and the location of the metastases. The average length of life for the operated animals was 8.4 days. In this series again, not a single animal showed the formation of metastasis. The high postoperative mortality and the somewhat shorter duration of life than in the animals of the first series, was probably due to the heat of the season. (These experiments were done in August.)

#### INOCULATIONS INTO THE BRAIN. THIRD SERIES

A few months later the experiments were again repeated. 18 animals were inoculated into the brain; in all the animals death was due to the intracranial growth of the tumor. Chart VIII shows the

duration of life of the animals, the comparative size of the primary tumor, and the frequency and location of metastases.

## CHART VI

## CONTROLS TO INOCULATIONS INTO BRAIN. FIRST SERIES

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	32	E	*	*	*	—	—	—	—	—
2	24	M	*	*	*	—	—	—	*	—
3	31	E	*	—	—	—	—	—	—	—
4	38	"	*	—	—	—	—	—	—	—
5	19	M	*	—	—	*	—	—	—	—
6	24	E	*	*	—	—	—	—	—	—
7	28	"	*	*	*	*	*	—	—	—
8	26	"	*	*	*	—	—	—	—	—
9	21	"	*	—	*	—	—	—	—	—
10	34	L	—	*	—	—	—	—	—	—
11	19	"	*	*	—	—	*	—	—	—
12	27	"	—	*	—	—	—	—	—	—
13	31	"	*	—	—	—	—	—	—	—
14	20	"	*	—	—	—	—	—	—	—
15	18	S	—	—	—	—	—	—	—	—
16	20	L	*	—	—	—	—	—	—	—
17	27	E	*	—	—	—	—	—	—	—
18	26	"	*	*	—	—	—	—	—	—
19	29	"	*	—	—	—	—	—	—	—
20	34	M	*	—	—	—	—	—	—	—
21	23	E	*	*	*	*	—	—	—	—
22	30	"	*	*	—	—	—	—	—	—
23	27	"	—	—	—	—	—	—	—	—
24	26	"	*	—	—	—	—	—	—	—
25	31	"	*	—	—	—	—	—	—	—
26	16	M	*	—	—	*	—	—	—	—
27	23	E	*	*	*	*	*	*	—	—
28	13	S	—	—	*	—	—	—	—	—
29	22	L	*	*	—	—	—	—	—	—

The average length of life was 12.5 days. Again no metastases were noted in any of the operated animals. No control animals were used for the second and third series of inoculations into the brain, since there were 78 control animals in this whole investigation available for comparison, and the behavior of the tumor in all the animals in which the inoculation was done in the pectoral muscle was quite similar.

In discussing the results of the experiments, it is advantageous to consider together the results of inoculations into the liver and into the gizzard as well as the controls, in which the tumor was inoculated into the breast muscle, and then to examine separately the results of inoculations into the brain.

As stated above, the tumor, when inoculated into the breast

muscle, grew to a large size, often completely destroyed the muscle tissue and the breast bone, invaded the peritoneal cavity, became disseminated there, and destroyed the vital organs. These animals, then, died of local malignancy, *i. e.*, through loss of function of some vital organ. In several cases, the metastases in the lungs completely replaced and destroyed the organs and thus caused the death

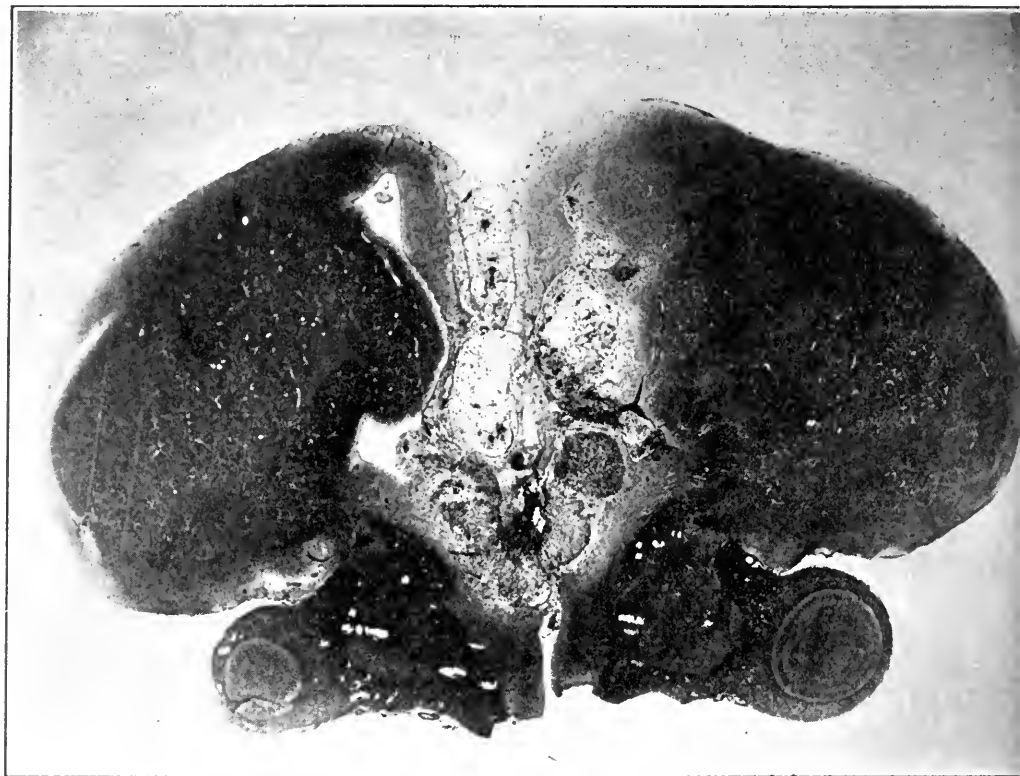


FIG. 3. Growth of sarcoma in brain of a fowl. Low magnification. Microphotograph.

of the animals. The duration of life of those animals in which the tumor was inoculated into the liver or gizzard was shorter than that of the animals inoculated in the chest wall, because in the animals of the first group the tumor immediately attacks and destroys vital organs. The operation as such does not seriously impair the condition of the animal, and if it is performed without inoculating the tumor the animals do not show any ill effects from the operation.

The behavior of the tumors inoculated into the brain is entirely different. The duration of life of the inoculated animals is shorter



CHART VII  
INOCULATIONS INTO BRAIN. SECOND SERIES

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intes-tine	Pan-creas
1	11	S	—	—	—	—	—	—	—	—
2	9	"	—	—	—	—	—	—	—	—
3	8	"	—	—	—	—	—	—	—	—
4	8	"	—	—	—	—	—	—	—	—
5	8	"	—	—	—	—	—	—	—	—
6	8	"	—	—	—	—	—	—	—	—
7	8	"	—	—	—	—	—	—	—	—
8	8	"	—	—	—	—	—	—	—	—
9	8	"	—	—	—	—	—	—	—	—
10	8	"	—	—	—	—	—	—	—	—
11	8	"	—	—	—	—	—	—	—	—

than that of the animals inoculated into the breast muscle, liver, or gizzard, but the tumor itself attains only a comparatively small size and does not metastasize. The smaller size of the brain tumors and the absence of metastases cannot be accounted for by the shortening of life of the animals through the inoculation, since during the same period of time (ten to fourteen days) much larger tumors develop and metastases occur when the inoculation is made in the liver (Chart I animals 2, 6, 8, 15, 16, 17) gizzard (Chart III animals 1, 9, 17, 20), or breast muscle (Chart IV animals 13, 16; Chart VI

CHART VIII  
INOCULATIONS INTO BRAIN. THIRD SERIES

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intes-tine	Pan-creas
1	17	S	—	—	—	—	—	—	—	—
2	16	"	—	—	—	—	—	—	—	—
3	14	"	—	—	—	—	—	—	—	—
4	13	"	—	—	—	—	—	—	—	—
5	8	"	—	—	—	—	—	—	—	—
6	15	"	—	—	—	—	—	—	—	—
7	10	"	—	—	—	—	—	—	—	—
8	17	"	—	—	—	—	—	—	—	—
9	10	"	—	—	—	—	—	—	—	—
10	11	"	—	—	—	—	—	—	—	—
11	13	"	—	—	—	—	—	—	—	—
12	11	"	—	—	—	—	—	—	—	—
13	9	"	—	—	—	—	—	—	—	—
14	11	"	—	—	—	—	—	—	—	—
15	11	"	—	—	—	—	—	—	—	—
16	10	"	—	—	—	—	—	—	—	—
17	14	"	—	—	—	—	—	—	—	—
18	11	"	—	—	—	—	—	—	—	—

animal 28). Neither does deficient nutrition explain this slight growth, since blood-vessels of comparatively large caliber are frequently observed within the tumors (Figs. 4, 5). Moreover, the pres-

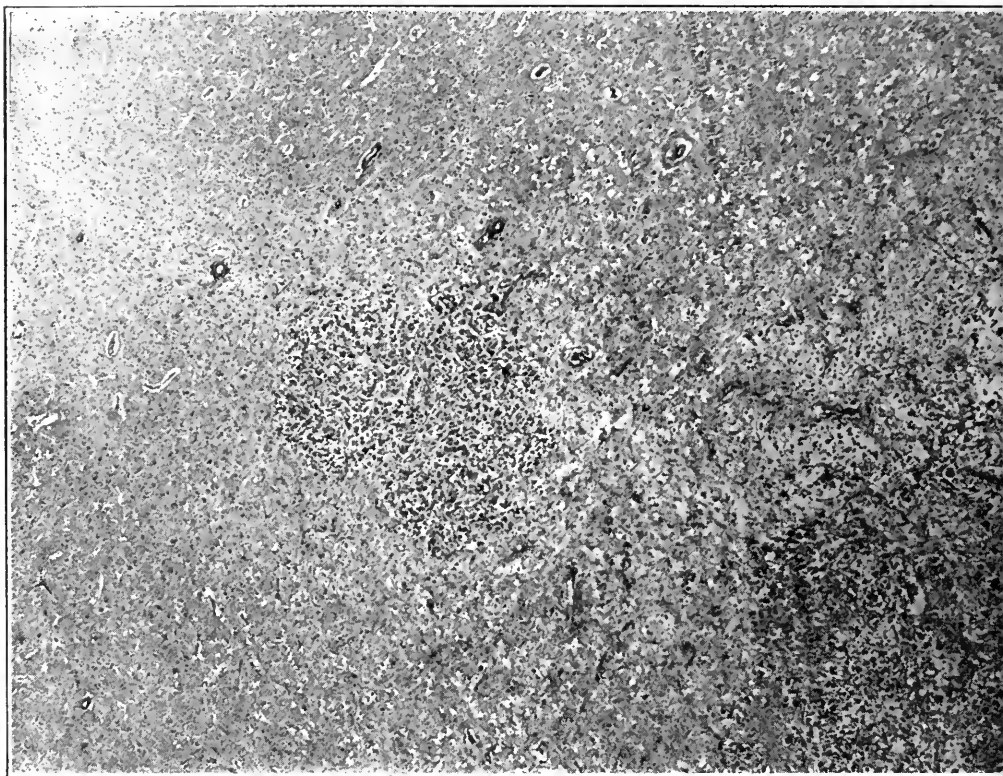


FIG. 4. Growth of sarcoma in the brain, showing bloodvessels. Microphotograph, low power.

ence of these blood-vessels indicates that it is as easy mechanically for the cancer cell to invade the blood-vessel and disseminate from the brain as from another locality.

The location of the growth within an osseous cavity also fails to explain the phenomena, since the tumor from the same source inoculated in the pectoral muscle, frequently breaks through the breast bone and invades the peritoneal cavity as early as two weeks after the inoculation.

The absence of metastases in the animals inoculated into the brain is not due to the lack of means of transportation of the tumor cells, since, as mentioned above, large blood-vessels are observed within the tumor growth. Neither can the small size of the tumors

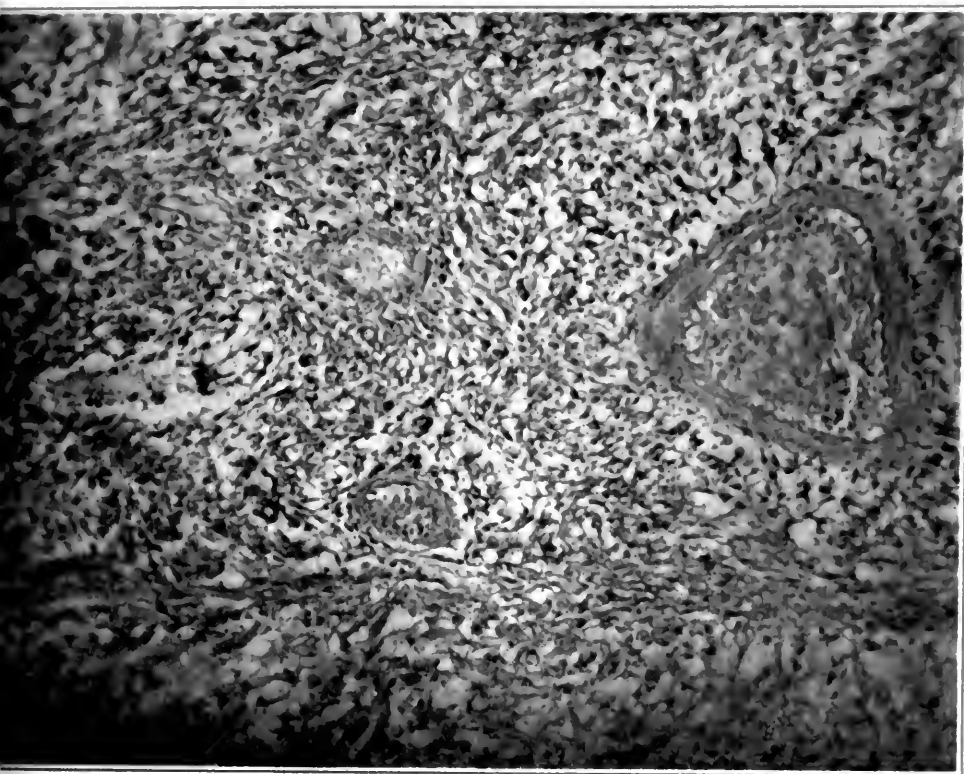


FIG. 5. Growth of sarcoma in the brain, showing bloodvessels. High power.

of the brain explain the absence of metastases. Metastases are observed in animals with small primary tumors in liver, gizzard or muscle (Chart I, animal 14; Chart III, animal 14; Chart VI, animal 28). A possible explanation of the scanty growth of the sarcoma in the brain and the absence of metastases may be found in the supposition that the brain tissue exercises a certain influence on the growth of the tumor.

#### REINOCULATIONS OF THE BRAIN TUMORS IN THE PECTORAL MUSCLE. FIRST GENERATION

In order to determine whether the immediate contact with brain tissue is the cause of the slow growth of the tumor cells it was thought desirable to observe the behavior of these tumors after re-inoculation from the brain into the breast muscle. 30 animals were used in these experiments. Chart IX shows the duration of life of

## CHART IX

## REINOCULATIONS OF BRAIN TUMOR. FIRST GENERATION

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intes-tine	Pan-creas
1	17	S	—	—	—	—	—	—	—	—
2	19	"	—	—	—	—	—	—	—	—
3	19	L	*	—	—	—	—	—	—	—
4	18	S	*	—	—	—	—	—	—	—
5	18	"	—	—	—	—	—	—	—	—
6	4	"	—	—	—	—	—	—	—	—
7	18	E	*	—	—	—	—	—	—	—
8	19	"	—	—	—	—	—	—	—	—
9	13	S	—	—	—	—	—	—	—	—
10	19	L	—	—	—	—	—	—	—	—
11	19	E	*	—	—	—	—	—	—	—
12	17	"	—	—	—	—	—	—	—	—
13	19	L	—	—	—	—	—	—	—	—
14	19	S	—	—	—	—	—	—	—	—
15	2	"	—	—	—	—	—	—	—	—
16	19	L	—	—	—	—	—	—	—	—
17	18	M	*	—	—	—	—	—	—	—
18	19	E	—	—	—	—	—	—	—	—
19	19	M	—	—	—	—	—	—	—	—
20	19	S	—	—	—	—	—	—	—	—
21	19	S	—	—	—	—	—	—	—	—
22	19	M	*	—	—	—	—	—	—	—
23	19	E	*	—	—	—	—	—	—	—
24	19	S	—	—	—	—	—	—	—	—
25	29	"	—	—	—	—	—	—	—	—
26	21	M	—	—	—	—	—	—	—	—
27	21	S	—	—	—	—	—	—	—	—
28	21	"	—	—	—	—	—	—	—	—
29	21	"	—	—	—	—	—	—	—	—
30	21	"	—	—	—	—	—	—	—	—

the animals, the size of the tumors, and the frequency and location of metastases. A comparison with Charts II, IV, and VI shows that while in these series the inoculations formed large tumors in 88.5 per cent. of the animals, and metastases were present in 78.5 per cent., the experiments presented in Chart IX show the formation of a large tumor in 33 per cent. of the animals and the presence of metastases in 23 per cent.

#### REINOCULATIONS OF THE BRAIN TUMORS IN THE PECTORAL MUSCLE. SECOND GENERATION

In this series of experiments the tumor for inoculation in the breast muscle was taken from the animals of the first generation described above. 18 animals were used for this series. Chart X shows a better result than Chart IX; large tumors were observed in 55.5 per cent. of the animals, and metastases were formed in 27.7 per cent.

### REINOCULATIONS OF THE BRAIN TUMORS IN THE PECTORAL MUSCLE. THIRD GENERATION

For this series of experiments the inoculation in the breast muscle was done with tumors obtained from the animals of the second generation reported above. 30 animals were used for inoculation. Chart XI shows the results of these experiments. 60 per cent. of the animals presented large tumors and 33 per cent. showed metastases.

The three series of reinoculations indicate that the power of the tumor to form large tumors upon inoculation, and to metastasize, is impaired during its growth in the brain and that subsequently this capacity for growth and the formation of metastases is partially recovered through subsequent reinoculations in the muscle.

CHART X  
REINOCULATIONS OF BRAIN TUMOR. SECOND GENERATION

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	19	L	—	—	—	—	—	—	—	—
2	19	S	—	—	—	—	—	—	—	—
3	19	L	*	—	—	—	—	—	—	—
4	19	S	—	—	—	—	—	—	—	—
5	19	"	—	—	—	—	—	—	—	—
6	19	M	*	—	—	—	—	—	—	—
7	19	L	—	*	*	—	—	—	—	—
8	19	"	—	—	—	—	—	—	—	—
9	19	"	—	—	*	—	—	—	—	—
10	19	"	*	—	*	—	—	—	—	—
11	19	"	—	—	—	—	—	—	—	—
12	19	"	—	—	—	—	—	—	—	—
13	20	S	—	—	—	—	—	—	—	—
14	18	L	—	—	—	—	—	—	—	—
15	20	S	—	—	—	—	—	—	—	—
16	20	"	—	—	—	—	—	—	—	—
17	20	"	—	—	—	—	—	—	—	—
18	20	L	—	—	—	—	—	—	—	—

As a result of this investigation the conclusion is reached that it is possible to inhibit artificially the power of proliferation and metastasis formation of a fowl sarcoma by inoculating it into the brain. A complete duplication of these experiments on inoculable tumors of white rats and mice is exceedingly difficult, since the latter tumors do not take so malignant a course as the fowl sarcoma. The inoculable tumors of the white rats and mice do not form metastases with any regularity and usually not sooner than six weeks after inoculation. The life of rats and mice inoculated subcutaneously is

also a great deal longer than the life of fowls inoculated into the breast muscle, while the life of any animal inoculated in the brain is short and does not average more than 10 days. As a consequence, the experiments with brain inoculation in mice and rats cannot be controlled satisfactorily by subcutaneous inoculations in the same animals.

The writer (23) was the first to inoculate tumors of white rats into the brain. The graft took in every animal but the size of the tumors was much smaller than that of a subcutaneous tumor, which would have developed during the same period of time. No further comparisons could be made between these two kinds of inoculations since the Ehrlich rat sarcoma, which was used for the experiments, does not form any metastases.

CHART XI  
REINOCULATIONS OF BRAIN TUMOR. THIRD GENERATION

Chicken Number	Days After Inoculation	Tumor	Metastasis							
			Lungs	Heart	Liver	Spleen	Kidney	Gizzard	Intestine	Pancreas
1	18	M	—	—	—	—	—	—	—	—
2	18	L	*	—	—	—	—	—	—	—
3	18	"	*	—	—	—	—	—	—	—
4	18	"	—	—	—	—	—	—	—	—
5	18	M	—	—	—	—	—	—	—	—
6	13	S	—	—	—	—	—	—	—	—
7	18	L	—	—	*	—	—	—	—	—
8	18	"	—	—	—	—	—	—	—	—
9	18	"	—	—	—	—	—	—	—	—
10	18	"	*	—	—	—	—	—	—	—
11	19	"	—	—	*	—	—	—	—	—
12	19	S	—	—	—	—	—	—	—	—
13	19	L	—	—	—	—	—	—	—	—
14	19	"	—	—	—	—	—	—	—	—
15	19	"	—	—	—	—	—	—	—	—
16	19	"	—	—	—	—	—	—	—	—
17	14	M	—	—	—	—	—	—	—	—
18	19	L	—	—	—	—	—	—	—	—
19	15	M	—	—	—	—	—	—	—	—
20	19	"	—	—	—	—	—	—	—	—
21	19	L	*	—	—	—	—	—	—	—
22	20	M	—	—	*	—	—	—	—	—
23	21	L	*	—	—	—	—	—	—	—
24	21	"	—	—	*	—	—	—	—	—
25	21	M	—	—	*	—	—	—	—	—
26	21	L	—	—	—	—	—	—	—	—
27	21	"	—	—	—	—	—	—	—	—
28	21	M	—	—	—	—	—	—	—	—
29	17	S	—	—	—	—	—	—	—	—
30	21	M	—	—	—	—	—	—	—	—

Investigations by other observers on inoculation of tumors in the brains of mice and rats have brought out certain facts which seem

to be in harmony with the results of the present investigation. Thus DaFano (24) observed that the energy of growth in intracerebral grafts seems to be somewhat lower than in other organs. Ebeling (25) found that when a graft from a subcutaneous carcinoma was inoculated into the brain of another animal it took in only 7.3 per cent. of the trials, while grafts from a brain tumor inoculated in brains of other animals took in 82 per cent. This difference in the takes the author attributes to the fact that the tumor gradually becomes adapted to the new soil. Here is apparently another instance in which the brain at first exerts an inhibitory influence on the development of the tumor. Ebeling further states that he saw no metastasis formation after inoculation in the brain, though it is not clear from his description whether the tumor which he was using produced metastases upon subcutaneous inoculation.

The mechanism of metastasis formation in malignant tumors consists of the following phases: (1) the detachment of a group of cancer cells from the primary tumor; (2) the transportation of this group of cells through the blood or lymph channels into distant parts of the organism; and (3) the proliferation of these cells in the new location and the consequent formation of metastatic tumors. This latter phase cannot be explained adequately by mechanical conditions and ease of transportation alone, and the possibility of interaction between the tumor cells and the cells of the various organs must be taken in consideration.

Such an interaction is quite evident in the case of a sarcoma of the fowl growing in the brain and is extremely probable in the case of malignant tumors of the rats and mice growing in the same organ.

#### REPORT OF CLINICAL CASES

The result of the experimental studies reported above indicates that the brain of a fowl has the power to depress the development of an inoculated particle of sarcoma tissue into a tumor; in other words it impedes the growth of the artificial metastasis, which every inoculation of a tumor into a lower animal practically represents. It is reasonable to suppose that the comparative infrequency of the formation of metastases in the human brain may also be due to the fact that the latter organ inhibits the formation of metastases, though the tumor emboli may have reached it.

The clinical investigations here reported also seem to bear out the opinion that metastasis in the brain is comparatively rare. During the last three years 3 cases of metastasis in the brain were observed, and certain peculiarities in the clinical course of the cases

may tend to support the deductions obtained from the analysis of the experimental study. It is advisable therefore to give a detailed history of the cases.

CASE I. Mrs. D. W. Age 41 years. Present illness began in August, 1914, with constipation, rectal tenesmus and loss of weight. 3 weeks after the onset of symptoms the patient entered St. Luke's Hospital. A diagnosis of carcinoma of the rectum was established and operations were performed, which consisted in a left inguinal colostomy followed 3 weeks later by sacral resection of the rectum. In December, 1914, the patient entered the Montefiore Home and Hospital. The examination on entrance did not reveal the presence of a recurrence, or of metastases of carcinoma anywhere. The general condition of the patient was good.

In July, 1915, the patient began to complain of general weakness. An examination through the colostomy wound showed a diffuse tumor mass in the peripheral segment of the sigmoid.

In August, 1915, the patient began to complain of severe headaches.

August 27, 1915. A neurological examination by Dr. I. Abrahamson showed no tenderness along occipital nerves, movements free, pains radiating around neck and into the cranium, and no radiation to the shoulder. Knee jerks lively on both sides. Achilles tendon reflexes exaggerated on both sides. No Babinski, no clonus. No evidence of any organic disease.

An ophthalmoscopic examination by Dr. A. Wiener revealed a choked disc in the left eye, outline of the right disc, hazy. There were small hemorrhages in the background.

September 23, 1915. Patient developed a transitory squint of the left eye and impairment of vision.

September 26, 1915. An ophthalmoscopic examination by Dr. A. Wiener revealed the following condition: Neuro-retinitis on both eyes. The backgrounds of both eyes show striated swelling with whitish patches. Incipient cataract of both eyes.

November 11, 1915. Patient shows bilateral convergent squint, suffers from nausea and vomiting and is delirious greater part of the day.

December 9, 1915. An ulcerated area appeared around the anus.

December 11, 1915. The sacral scar opened along its entire length. On separating the skin flaps, the underlying tissue of the sacral region is covered with a dirty grayish substance, which on the touch appears to be firmly adherent to the deeper layers of tissue. The condition presents the picture of a moist gangrene.

December 17, 1915. Destruction of cornea and xerosis developed in the right eye and xerosis and diplopia of the left.

On December 25, 1915, the patient died.

The autopsy was performed 52 hours post mortem by Dr. R. A. Lambert and the following is the report:



## ANATOMICAL DIAGNOSIS

Recurrent carcinoma of rectum with extension to perirectal tissues and uterus. Metastases to retroperitoneal and cervical lymph glands, thyroid, lungs, meninges and brain. Acute cystitis and pyelonephritis. Old tuberculous foci in bronchial lymph nodes. Emphysema (moderate). Extreme emaciation. Ulcers of cornea.

The body is that of an elderly woman measuring 153 cm. in length, showing extreme emaciation. Post mortem rigidity present. Moderate hypostasis—present in dependent parts. The skin of the abdominal wall shows a bluish discoloration. In the left inguinal region there is a healed colostomy wound showing slight excoriation of the skin in the immediate neighborhood. The opening is about  $1\frac{1}{2}$  cm. in diameter. In the midline of the abdominal wall, extending from the pubis to a point about 3 cm. below the umbilicus, is an apparently old, perfectly healed, surgical wound. There is extreme atrophy of the muscles everywhere, especially marked in the extremities. No edema of the legs. The nails show distinct lateral and longitudinal curving, but there is no clubbing of the fingers. The superficial lymph nodes are nowhere readily palpable. The thorax appears somewhat rounded and prominent, probably on account of the great emaciation. The breasts are quite atrophic. No nodules are felt in them. There are no definite skin lesions anywhere and no nodules in the skin or superficial tissue. (The rectum and anus were removed at operation—see clinical history notes.) In place of the anus there is a wide opening measuring at least 3 cm. in diameter which leads into a kind of smooth-walled sac in the lower pelvis. There is no discharge from this opening. All the upper teeth are absent, except one molar at the right side. Some of the lower teeth are carious. No discharge from nose or ears. The cornea of the right eye is completely sloughed away and the eyeball beneath feels soft and flabby. The sclera is rather opaque and injected. The left eye shows a marked opacity of the cornea with apparently superficial ulceration. The conjunctivæ very slightly injected.

*Abdomen.*—The intestines in general are freely movable. There are no old adhesions except in connection with the sigmoid and rectum (to be described later). The liver extends about 2 cm. below the costal margin in the right mammillary line. The spleen lies high up in the costal arch. The mesenteric lymph glands are not very large but feel rather firm.

*Thorax.*—The thymus appears to be completely atrophied. There is practically no fat in the mediastinum. The left lung is not adherent anywhere. The right is bound to the chest wall by old adhesions over almost its entire surface, with the exception of its anterior margin. The pericardial cavity contains a slight excess of clear straw-colored fluid. The thoracic duct is not readily found, but pretty certainly not obstructed.

*Heart.*—The heart weighs 220 gm. The cusps of the tricuspid and pulmonary orifices are quite thin and delicate, show no vegetation. There is slight thickening in places near the margin of the

mitral leaflets, and they show also a few patches of atheroma. The aortic cusps are delicate. There are quite a number of arteriosclerotic patches in the sinuses and these extend also to the leaflets of the valve. In the coronaries a few arteriosclerotic patches are found. None of the chambers of the heart are dilated: the musculature is pale: no scars are found. The aorta is fairly elastic, and very few arteriosclerotic patches are found. These are chiefly of a fatty nature and are more numerous in the lower abdominal portion.

*Lungs.*—The left lung weighs 275 gm. It is quite collapsed. The pleura is thin and smooth everywhere. In places there is an excessive accumulation of pigment. On palpation several hard nodules are felt, chiefly in the posterior portion of the lower lobe. There is one in the lower portion of the upper lobe, just anterior to the hilum. On section these nodules are especially marked off from the adjacent lung tissue, and are exceedingly hard. They are made up of radiating strands of early connective tissue which separate in yellow foci of varying size. They are evidently metastatic tumor nodules with, in places, necrosis of the larger nests of tumor cells. The bronchial lymph nodes are heavily pigmented, and on section one of them shows an old caseous tuberculous focus. The largest of the nodules measures about  $2\frac{1}{2}$  cm. in diameter. They are roughly spherical in shape. There are no tumor nodules in the pleura, although in one place the mass in the lung appears to be attached to the pleura. The bronchi and blood vessels appear to be practically normal. The picture of the lung is rather coarse, and along the anterior margin there are several lappets of emphysematous lung tissue.

The right lung weighs 450 gm. The pleura everywhere presents tags of old adhesions, fibrous. On section several large tumor nodules are found in the lower lobe. These measure from 3 to 5 cm. in diameter. They are similar to the smaller nodules in the other lung. In the upper lobe there are several similar nodules, and some areas which are quite different. They are firmer than the adjacent lung tissue, gray in color and slightly translucent. It is difficult to say whether these are patches of pneumonia or invasion of the alveoli by tumor—a sort of “cancerous pneumonia”—where the tumor cell fills the alveolar spaces—the septa remaining practically normal.

*Liver.*—The liver weighs 1,100 gm. and measures  $22 \times 16 \times 8$  cm. It is normal in shape, except that the gall bladder notch is exaggerated. The capsule is thin and smooth. The lobulation is visible, but the lobules do not stand out clearly. The periphery is gray and the center grayish-red. No tumor nodules are found.

*Spleen.*—The spleen weighs 85 gm. and measures  $11 \times 6 \times 3$  cm. The capsule is wrinkled, not thickened. The organ is soft, doughy, in consistence. On section the cut surface retracts from the capsule. The follicles are numerous, fairly well outlined: the trabeculae are possibly a little thickened: no tumor nodules found.

*Pancreas.*—No fibrosis and no marked fatty replacement.

*Adrenals.*—The adrenals are rather large, each weighing approximately 20 gm. On section they are normal.

*Kidneys.*—The left kidney weighs 120 gm. The fetal lobulations have persisted. The capsule on removal leaves a smooth surface. The cortex measures about 7 mm. The markings in most places are distinct. The tissue is pale, especially the cortex. The pelvis appears to be slightly dilated. No tumor nodules or abscesses are seen.

The right kidney weighs 140 gm. On removing the capsule a number of irregular yellowish gray foci are seen shining through. They appear to be slightly elevated. On section these areas extend through the cortex into the pyramids, where they are more numerous and appear as pearly yellow lines running toward the pelvis. These are clearly abscesses. In places where these abscesses are absent a normal architecture is presented. There is slight dilation of the pelvis: its mucosa is injected but apparently not ulcerated anywhere.

*Pelvic Organs.*—The bladder is contracted, the mucosa is of deep red color and edematous in places here and there. The epithelium appears to have disappeared. The musculature on section looks fairly normal, so that the inflammatory process is probably recent. (Urine was normal up to 10 days before death.) Uterus—normal in size. Small myoma about 4 mm. in diameter is found in the fundus, just beneath the peritoneum. On the posterior side there appears to be an invasion of the uterine wall by tumor mass growing in the rectum. The vagina-mucosa is somewhat congested, otherwise normal.

*Neck Organs.*—Palate, tongue, larynx and trachea normal. The thyroid—the right lobe somewhat enlarged and hard on section; it is seen to be almost completely replaced by a tumor nodule of the same character as that observed in the lung. The left lobe shows also a tumor nodule occupying about half the organ. In the right upper cervical region a hard lymph node is found, measuring about  $1 \times .6$  cm. in diameter which on section is found to be occupied by a metastatic tumor growth.

*Alimentary Tract.*—The esophagus is normal. Stomach—there are a few hemorrhages in the mucosa not far from the pylorus. In addition to this there is a circumscribed area about 2 cm. which suggests early ulcer, but may be only post mortem (block taken). Small intestines—normal. Large intestine—the sigmoid flexure is attached to the abdominal wall, and shows an opening to the outside (see note above—colostomy wound). The sigmoid ends in a blind pouch in the pelvis, which is probably the upper end of the amputated rectum. There is a marked dilatation of this sac, which is almost filled with a necrotic, fungating, ulcerating mass which springs up from its bottom. The growth, which is clearly neoplastic, extends through the wall of the intestine into the perirectal tissue, and to a slight extent into the posterior wall of the uterus.

*Bone Marrow.*—The bone marrow is yellowish red in color, rather opaque.

*Brain.*—The brain removed and placed immediately into formalin. In the pia covering the upper portion of the right hemisphere of the cerebellum there is a small nodule about 1 cm. in diameter which has pressed inward and occupies a depression in the cere-

bellum itself. It is possible to palpate several hard masses in this cerebellar hemisphere, although they do not extend quite to the surface. In the upper posterior position of the frontal lobe of the cerebrum similar hard nodules are palpable. The hypophysis appears normal. No tumor nodules are found in either the orbit or about the optic nerves.

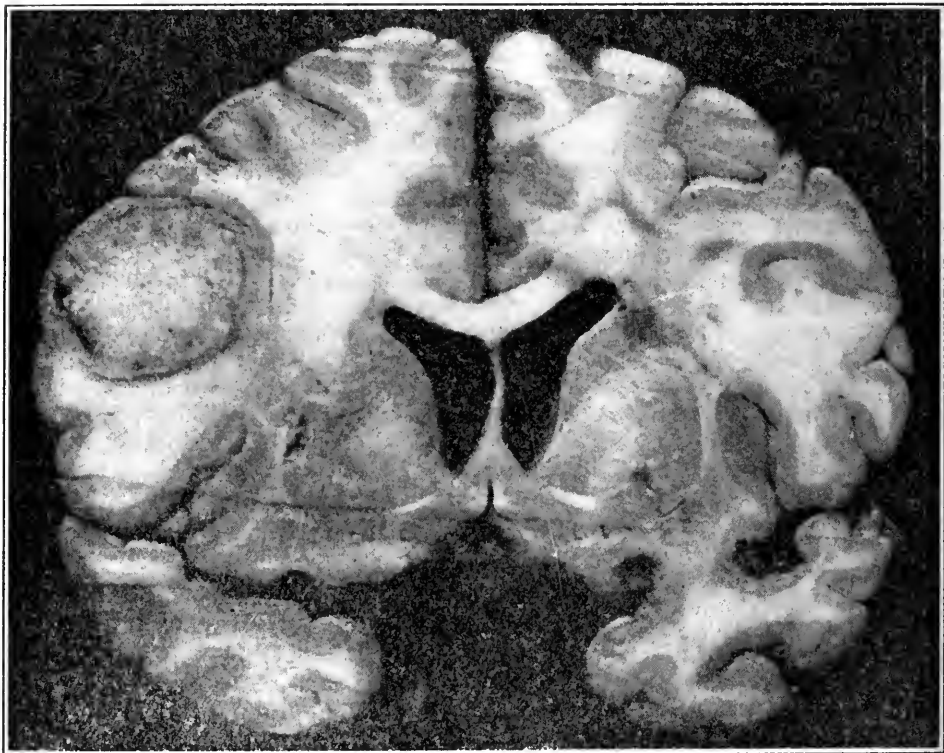


FIG. 6. Gross photograph of a frontal section of the hemispheres passing through of the anterior commissure showing a metastasis in the right hemisphere.

On a frontal section of the hemisphere passing through the middle anterior commissure there is a metastasis in the right hemisphere (Fig. 6), there are also two metastases found in the right occipital lobe (Fig. 7) and two metastases in each hemisphere of the cerebellum (Fig. 8).

CASE II. Mrs. A. B. Age 45 years. Present illness began a year ago with pain in the left hand, radiating down from the shoulder. She consulted a physician, who called her attention to little lumps in the left breast. She went to Mount Sinai Hospital, where her left breast was amputated. After leaving Mount Sinai she experienced great pains in various regions of her body, chest, legs, back, etc. The pains grew progressively worse, until 6 months



FIG. 7. Gross photograph of a section of the right occipital lobe, showing 2 metastases.

later, she went to Gouverneur Hospital, where she stayed 14 days. She became gradually weaker, paler and complained of headaches, pains in various regions of body, loss of weight, and impairment of vision.

On October 1, 1915, the patient was admitted to the Montefiore Home and Hospital.

On admission the patient presented the following status: notable protuberance of eye balls, anxious expression. On the left side of the chest there is a scar of a radical breast amputation. In the axillary line of scar there are a few subcutaneous nodules of recurrence; also one nodule at the lower part of the axilla. No lymph nodes enlarged anywhere. Severe pain on pressure at the right elbow



FIG. 8. Gross photograph of a section of both hemispheres of the cerebellum, showing 4 metastases.

joint. Same amount of pressure does not elicit as much pain at left elbow joint. No pain or deformity at hip joints. No pain along femurs.

A metastatic subcutaneous nodule is noted over the region of the left scapula.

Arm jerk elicited on right. Knee jerk increased on right. No Babinski, but marked Oppenheim on right, also present on left. Hemifacial paresis. Atrophy of right upper extremity including intrinsic muscles of hand.

October 14, 1915. An ophthalmoscopic examination by Dr. A. Wiener showed the following condition:

*Right Eye.*—Disc is blurred. Very few of the vessels can be seen in the disc, on account of the edema and hemorrhage. These hemorrhages are flame-like and streaked in appearance and extend beyond the periphery. There are some round hemorrhages. There are no exudations. The appearance just beyond the disc is pinkish and grayish white, due to edema. There are hemorrhages scattered around the macula, some superficial and some deep. The whole picture is one of thrombosis of central vein.

*Left Eye.*—On the outer portion of fundus, distinct detachment of retina well defined, showing vessels creeping directly over it; looks like a solid mass whitish in appearance and in periphery down below, are scattered hemorrhages over the mass. The disc cannot be seen. All outlines are blurred, its position being occupied by a star shaped pinkish white mass, dotted with streak like hemorrhages. Emerging from this mass one can see here and there some blood vessels. There are hemorrhages scattered about fundus, but the whole fundus is more or less indistinct.

*Significance.*—May be explained by metastasis occupying the outer portion of fundus, and either a papillitis pure and simple, or a metastatic infiltration of the nerve.

An X-ray examination of nearly the whole skeleton of the patient was made with the following results:

*Hips.*—Marked irregular bone destruction of the upper half of both femora, and all the bony parts of the hip joints.

*Shoulders.*—Advanced irregular bone absorption of all the bones entering into the formation of the shoulder joints.

*Ribs.*—The posterior portion of almost all the ribs, especially on the left side, shows a great number of spots of bone destruction.

*Skull.*—All the bones of the skull show a great amount of irregular bone destruction of both tables.

All the abnormalities in the skeleton stated above were due to multiple metastases of carcinoma in the bones.

December 24, 1915. Patient in clonic convulsions, duration about 2 to 3 minutes, no froth.

December 30, 1915. The palpation of the skull shows a protuberance over the left temporal region, consisting of a soft diffuse mass, about 2 inches in diameter (a massive bone metastasis).

Palpation of left side of chest wall is painful. Second, third and fourth ribs feel rough nodular. The left knee joint is swollen and painful. An enlargement is apparent on the head of the tibia.

An indistinct swelling is present in the lumbar section of the spine.

January 13, 1916. A swelling has developed in the middle of the right clavicle, which is soft on palpation and indicates a complete destruction of the bone in this section of the metastatic area.

January 19, 1916. Patient's speech is not clear, slow and confused. Complains more of pain than heretofore and in addition to the swellings already found she developed a swelling over the right Poupert's ligament, which is soft, doughy and easily compressible, but not tender.

January 22, 1916. Patient was unconscious for the last 2 days.

The patient died on January 22, 1916. An autopsy could not be obtained. The presence of metastases in the bones were proven by palpation and X-ray examination, metastases in the left eye were shown by an ophthalmoscopic examination and metastasis in the brain appeared quite certain from the clinical course of the disease.

CASE III. Miss R. S. Age 42 years. A radical amputation of the right breast was performed in August, 1915, for carcinoma with involvement of axillary and supraclavicular lymph glands. Four months later there has developed a kyphosis, a swelling at the regions of both trochanters and inability to walk.

Two months later the patient began to complain of severe headaches, became delirious, then developed a right hemiplegia which was followed by death two days later. No autopsy could be obtained, but the patient unquestionably died of a metastasis in the brain.

The characteristic feature of the three cases of metastasis of carcinoma of the brain described above consisted in the extensive metastatic dissemination of the carcinoma in various organs and in the extremely severe course which the disease took. The symptoms of the metastasis in the brain appeared comparatively late in the course of the disease. The impression may be gained from the analysis of these cases that the brain resists the invasion of the carcinoma longer than the other organs. Lung involvement apparently took place in two of the reported cases. The frequency of the involvement of the lungs observed in cases of metastases of carcinoma of the brain is taken by some authors to indicate the importance of mechanical conditions for the formation of these metastases. It is presumably easy for carcinoma emboli from the lungs to reach the brain. The weak point of this hypothesis consists in the fact that metastases in the lungs are found in over 25 per cent. of cases of carcinoma, while metastases in the brain, as stated above, are found in only 4.77 per cent. of cases. In other words only a small number of the cases of carcinoma which develop metastases in the lungs also metastasize in the brain.

Metastases in the cord are even less frequent than metastases in the brain. The writer found only seven cases of metastases in the cord reported in literature, and of these only one case that of Taniguchi (18) was described in detail.

Comparatively more frequent are metastases in the meninges and in the spine. The latter condition is of interest both from the theoretical and the clinical standpoint. The theoretical importance of the condition consists in the fact that while the metastatic tumor destroys the vertebræ, grows into the spinal canal and causes clinical symptoms of compression of the cord it does not invade and form a metastasis in the latter organ. Apparently here is another instance of the resistance of nerve tissue to the growth of carcinoma. Clinically these conditions must be classed not with skeletal metastases but with metastases in the central nervous system, since they very early give rise to symptoms characteristic of tumors in the central nervous system.

Three such cases came under observation of the writer recently.

CASE IV. Mrs. B. F. Age 56. Admitted to the Montefiore Hospital on July 6, 1915.

*Present History.*—Patient relates that while walking along a street she fell, could not rise and had to be carried to the house. She was treated at home for a while, then taken to the Lebanon Hospital where a plaster cast was put on. She wore this cast for 5 months, and when it was removed, she was unable to walk or stand.

*Physical Examination.*—On admission showed the following condition: The patient is very restless, markedly emaciated, unable to walk or stand. *Lungs*—right hyperresonant; left—dull on percussion anteriorly and posteriorly, flat at base. On auscultation, broncho-vesicular breathing at apex anteriorly and bronchial breathing lower down. Posteriorly breathing is intensified at apex. Diminished breathing at middle, and almost absent breathing at base. *Inguinal glands* enlarged on left side. *Spine*—marked tenderness over lower dorsal and upper lumbar spine; entire spine is very rigid.

July 12, 1915, entire left lung dull, on auscultation posteriorly breathing almost absent at base; bronchial breathing in left axilla.

The patient died on July 25, 1915. The autopsy was performed by Dr. Pappenheimer, 24 hours post mortem. The following is the report.

*Pathological Diagnosis.*—Primary adenocarcinoma of lung, metastasis in pleura, liver, adrenal, ribs, vertebræ, lymph gland in left axilla. Chronic pleuritic adhesions and suppurative pleurisy (left side). Bronchiectasis, suppurative pericarditis, duodenal ulcer, brown atrophy of viscera, slight compression of filum terminale and cauda equina by metastases in 2d lumbar vertebra.

The body is that of an elderly woman measuring 150 cm. in length and of slight frame. There is much general emaciation.



The breasts are flabby and atrophic. The eyes are sunken, the pupils equally contracted. Most of the teeth are carious, only a few stumps remaining. The mucous membrane is extremely pale.

The abdomen is slightly prominent and shows post-mortem discoloration. Rigidity is present in all limbs. The subcutaneous fat is less than 1 cm. in thickness.

The peritoneal cavity contains only a small amount of blood-stained fluid. The large gut, especially the cecum and sigmoid, is much distended with gas. There are fibrous adhesions between the ascending colon and the transverse colon, the latter is much elongated and extends as far down as the symphysis. The stomach is contracted and reaches to about the umbilicus. The spleen extends to the edge of the ribs. The left lobe of the liver reaches 7 cm. below the ensiform cartilage, the right lobe about 2 cm. below. The diaphragm extends to the lower border of the 5th rib at the left, and is convex at its inferior surface.

On removing the sternum the right lung is found to extend slightly beyond the median line over the upper lobe. It is adherent by organized bands to the pericardium and very firmly along the posterior border to the chest wall, particularly over the apex. The pericardial sac is considerably distended, it contains 60 c.c. of turbid brownish fluid, in which are many coarse flakes and threads of fibrin. Left thoracic cavity—the lung is very much shrunken and bound down most firmly to the pleura in the upper portion of the thoracic cavity. The greater part of the left pleural cavity is filled with a very thick chocolate viscid fluid containing many large threads of soft fibrin.

*Heart.*—The heart weighs 300 gm. The epicardium is rather dull, and covered in places by a firm fibrinous exudate. Over the anterior surface of the right ventricle there is a large tendinous patch, and over the posterior surface of the left ventricle the epicardium is much thickened, but quite opaque. There has obviously been some atrophy of the epicardial fat, as the vessels are quite tortuous. The right auricle is distended with cruor. The foramen ovale is closed. The tricuspid ring measures 13 cm. The edges of the valves seem a little edematous. No marked deformity. The right ventricle is about 2 to 3 mm. in thickness. The pulmonary ring is 8 cm. The cusps are normal. The mitral ring measures 8 cm. in circumference. The valves are normal. The aortic opening measures 7 cm. The cusps are normal. The muscle of the left ventricle is quite thin near the apex, 1 cm. or less; it is rather flaccid and distinctly brownish. The coronaries are wide and not sclerotic. The ascending portion of the aorta is inelastic, showing a few slightly sclerotic patches.

*Lungs.*—The right lung is voluminous and weighs 600 gm. There are adhesions at the apex and between the lobules. One can see through the pleura very numerous slightly elevated translucent grayish plaques, which appear to lie beneath the pleura rather than in it. They do not obviously follow the pleural lymphatics. None of them are more than 2 or 3 mm. in size. They are not distinct in

the posterior portion of the lower lobe. The bronchi contain frothy yellow fluid, and are somewhat congested. On section, both the upper and lower lobes appear to be studded with numerous miliary nodules, which are felt even more distinctly than they can be seen. They are all quite well circumscribed, translucent, firm and not caseous. There seems to be rather more scar tissue in the upper lobe than elsewhere. There are no definite tuberculous foci. The bronchial lymph nodes are large and pigmented.

The left lung weighs 520 gm. The entire lung is covered with a very thick opaque but rather smooth pleura, which can be separated from the lung only with effort. On section both the upper and lower lobes are found to be only slightly air-containing; they contain a good deal of pigment. Just above and below the remains of the inter-lobular septum there is a large irregular cavity filled with turbid brownish fluid. Scattered through the remaining lung tissue there are occasional fairly distinct small grayish nodules. The small blood vessels and bronchi are thickened and project above the surface. The texture of this contracted lung tissue is exceedingly leathery. The lymph nodes at the hilum are pigmented.

*Liver.*—The liver weighs 1,050 gm. and appears shrunken, the capsule being wrinkled in many places. The right lobe is crossed by a deep linear fissure which extends as scar tissue a short distance into the liver substance, but only in its central portion. Scattered quite regularly through both lobes, one can see both superficially and on section grayish nodules sharply circumscribed, composed of uniformly firm, almost pearly tissue, showing no central necrosis. The nodules are not surrounded by zones of injection—the largest does not exceed 1 cm. in size, and the smallest 1 or 2 mm. The rest of the liver tissue shows rather more central stasis. The lobules are a little irregular.

The *gall bladder* is distended with thick viscid black bile. The mucosa appears normal. The ducts are patent.

*Spleen.*—The spleen measures  $10 \times 6\frac{1}{2} \times 3$  cm. The capsule is wrinkled and very thick. The spleen weighs 100 gm. The pulp is firm and pale with very well marked trabeculae and thickened blood vessels. The follicles are quite indistinct.

*Kidneys.*—The *left* kidney—the capsule adheres somewhat, carrying some of the kidney tissue with it, and leaving a pale granular surface, with rather deep stellate scars. The cortex is slightly narrow, averaging about 4 mm. The striations are quite distinct, but interrupted in places and a little diffuse. The glomeruli are indistinct. The color is grayish yellow, with a somewhat dark pyramid. The *right* kidney is somewhat more congested, but otherwise similar. Together, the kidneys weigh 200 gm.

*Pelvis and Uterus.*—Normal.

*Adrenals.*—The *left* adrenal is normal in size; has a very translucent cortex with yellow points and streaks, but one portion of the gland seems rather largely replaced both in the cortex and the medulla by grayish white tissue. The *right* adrenal also contains tumor tissue in the upper pole.

*Bladder.*—The bladder shows injected venules in the region of the trigonum particularly, and here the mucosa is distinctly granular. There are venules also in the urethra, with small hemorrhages.

*Vagina.*—The vagina shows very congested mucous membranes with plaques of keratosis in the vulva. The cervix is drawn over to the right and in the right vaginal fornix, beneath the mucosa, there is an ill-defined mass of very firm grayish white tissue. The cervix itself is long. The external is rather scarred. There are numerous Nabothian cysts visible through the mucous membrane. The lining of the corpus uteri is extremely smooth and the cavity contains a slightly turbid thin fluid. The tubes show nothing abnormal. The ovaries are very dense, sclerotic and contain numerous corpora albicantia. The peritoneum lining the cul-de-sac is much thickened and puckered by adhesions.

*Rectum.*—The rectum contains large scybala. The mucous membrane is normal.

*Aorta.*—The aorta shows a moderate sclerosis of the usual type. The thoracic and abdominal portion is quite elastic.

*Stomach.*—The stomach is quite contracted, the mucous membrane is normal.

*Duodenum.*—The duodenum at a distance of 4 cm. from the pyloric ring, is the seat of a circular ulcer about 1 cm. in diameter with a firm cartilaginous base.

*Pancreas.*—The pancreas is normal.

*Intestines.*—The intestinal tract is normal.

*Esophagus.*—Normal.

*Breasts.*—The breasts on section are rather flabby and atrophic, but show no tumor tissue. There is a very hard calcareous gland about the size of an almond in the right inguinal region.

*Tongue.*—The tongue is covered with a thick yellow fur. The base of the tongue is smooth. The *pharynx* is normal. The *larynx* and *trachea* are normal. The *thyroid* is symmetrical and presents the normal appearance of a colloid gland, on section.

There is a marked right lateral curvature. The spinous processes of the first few sacral vertebræ seem to be rather prominent, and with the patient in the prone position the spinal column curves rather forward just above this region. There is found lying to the right of the cord, in the region of the 2d and 3d lumbar vertebræ, a mass of soft, grayish tumor tissue—this has deflected the cord to the left, and apparently caused a distinct flattening and compression of the cord at that point. This tumor on microscopic examination was found to be an adenocarcinoma, identical with the tumor in the lungs.

CASE V. Mrs. R. R. Age 43 years. Admitted to the Montefiore Home and Hospital January 16, 1916. Present illness began May, 1915, when the patient noticed a very small lump, the size of an orange seed, underneath the skin of the left breast which grew no better in spite of various salves. In August the breast was amputated at Beth Israel. In October the patient began to complain of pain in lower extremities and back.

*Physical Examination.*—The patient showed excess of subcutaneous fat. The lungs and heart showed no abnormalities. There is a scar of a radical breast amputation over the left chest. A hard smooth mass is felt reaching from the mid axillary to the mid clavicular line on the left chest. There are also open wounds here bleeding freely. The liver reaches to F. B. above C. M. in R. M. L. There is a bed sore in the upper portion of the left thigh. Tenderness over both thighs.

January 13, 1916, tongue protruded to the right of mid line. To the right of the sternal end of the scar is a round, ulcerated area about  $1\frac{1}{4}$  in. in diameter, the surface slightly elevated. Other ulcerated areas present over the left side of the chest. In the skin there are numbers of shot-like, hard nodules. No lymph glands palpable in either axillæ, supra- or intra-clavicular regions. The liver not enlarged. Pressure over the upper third of left femur causes pain. Pressure over the spine extremely painful.

January 1, 1916. A small superficial bed sore has developed on each buttock. The patient's mind not clear.

January 17, 1916. Partial paralysis of the tongue and the peculiar slowness and abnormality of the speech bring to mind the possibility of the beginning of a metastatic growth in the nervous system.

X-ray January 20, 1916: Eleventh and twelfth dorsal vertebræ showed great absorption of bone. The entire lumbar spine has a worm-eaten appearance. The upper portion of the neck of the right femur presents a combination of bone condensation and absorption. Chest shows markedly diminished aëration of the middle lobe due to small-sized nodular infiltration. The skull shows spots of irregular frontal bone destruction. Abnormally high diaphragm on the right. No evidence of bone destruction of the ribs.

Patient died on February 13, 1916; the autopsy was performed by Dr. B. S. Kline, 25½ hours post mortem.

#### ANATOMICAL DIAGNOSIS

Carcinoma of breast with recurrence in wound following removal. Metastases to the regional lymph glands, liver, bone, pancreas, lung. Anemia, fatty change of heart muscle, kidneys, liver. Pulmonary emphysema, calcification of bronchial lymph nodes, fibrous pleural adhesions, subserous and submucous fibromata of uterus, colloid adenomata of thyroid, chronic and acute tonsillitis, decubitus ulcers, pulmonary edema.

The body is that of a moderately obese woman, 152 cm. in length, rigor no longer present in the extremities. Moderate hypostasis. Skin and mucous membrane pale. There is a large ulcer over the sacrum, about  $10 \times 6$  cm., a portion of which extends deep into the subcutaneous tissues, the base is covered with foul smelling, necrotic tissue. A smaller more superficial ulcer is seen on the left buttock, and another over the fourth dorsal vertebra of spine. There is a large scar extending across the left anterior chest into the axillæ, healed except in the anterior axillary portion where there is an open-

ing a few cm. in diameter connecting with the sinus which extends deep into the muscular tissues of the upper arms and chest wall. The sinus is filled with a slightly blood tinged, sero-purulent fluid. In the skin of the left anterior chest there are many discrete and confluent, pearly gray, firm nodules. The skin in places is ulcerated. The cervical lymph glands palpable.

*Head.*—Shows no abnormalities. *Eyes*—palpebral slits narrow. The pupils moderately dilated, equal, slight arcus senilis in each eye. *Ears, Nose*—no abnormalities. *Mouth*—few teeth gone from each jaw, remainder showed erosion of edges, a few showed a moderate to extensive caries. There is moderate infiltration of the gums. *Neck*—no abnormalities.

*Chest.*—Well formed, superficial veins over the upper anterior portion dilated. The right breast, large, firm dome; no solid masses palpable.

*Abdomen.*—Normal externally. External genitalia showed no definite abnormalities.

*Extremities.*—Well formed.

On making the skin incision, a large amount of glistening yellow fat is found in the subcutaneous tissue. On opening the abdominal cavity, the omentum is found of good size, somewhat rolled up, free. The organs normally disposed. The liver reaches to costal margin. The appendix shows adhesions in proximal portion, free distally. The fundus of the uterus and both ovaries lie above the pubic brim. The peritoneum, in an area near the body of Douglas, shows numerous small, discrete, black spots, suggesting old hemorrhages. The diaphragm reaches to the 2d space on the right, 3d on the left.

*Thorax.*—The anterior borders of the upper lobes retracted a few cm. from the mid line. No adhesions or fluid in the right sac. There are rather thin, fibrous adhesions along the whole anterior border of the left upper lobe, binding the lung to the chest wall and pericardium. A number of fibrous adhesions between the lower inferior medial portion of the upper lobe and the chest wall. There is no excess of fluid. The thymus atrophied, replaced by fat. The pericardial sac is free of adhesions and excess of fluid, the membrane pale.

*Heart.*—The heart weighs 270 gm. There is a considerable amount of greasy yellow fat below the epicardium. The epicardium is thin and glistening everywhere. The right auricle is of average size and thickness. The endocardium thin; there is some post-mortem discoloration of it due to blood. The fossa ovale closed. The tricuspid valve and chordæ thin and puckered. The right ventricle of average size and thickness; the endocardium thin. The muscle flap pale brown. The pulmonary valve cusps thin and delicate; the base of pulmonary artery smooth. The left auricle somewhat dilated, slightly thickened. The endocardium is as usual. The mitral valve and chordæ thin. The left ventricle slightly dilated. The papillary muscles somewhat flattened. The endocardium thin and glistening. The aortic valve cusps thin and delicate. The base of the aorta smooth except for a few small soft, yellow opaque patches in

the intima near the valve. There is some post-mortem discoloration due to blood within the intima. The coronary vessels are not tortuous, the walls of average thickness. There are, however, numerous soft yellow, opaque patches in the intima of all branches, together with post-mortem discoloration due to blood. The myocardium of the left ventricle is soft, flabby, uniformly pale and brown. Fibers and bundles of average thickness.

*Lungs.*—*Right lung* weighs 400 gm. The lobes fairly voluminous, moderately cushiony and inelastic; in addition, they feel slightly soggy. The pleura everywhere thin and glistening. The lymph glands at the hylum, firm and pigmented. Vessels and bronchi show no definite abnormalities. On section a moist, pinkish red surface present in all lobes. On pressure a small amount of thin, frothy fluid exudes from the air spaces. In the center of the upper lobe there is a small pea-sized, fairly firm, irregular, gray nodule, suggesting a tumor metastasis. The posterior portion of the lower lobe is somewhat collapsed, containing no air, deep red in color. *Left lung* weighs 350 gm., fairly voluminous, cushiony and inelastic. The posterior portion of the lower lobe is somewhat collapsed. The pleura in general thin and glistening. There are, however, some tags over the lower anterior portion of the upper lobe. The lymph glands at the hylum are moderately enlarged, firm and pigmented. Two of them show several small areas of calcification. The vessels and bronchi show nothing unusual. On section the lung presents a similar picture to that of the right. There is a small, irregular gray nodule in the center of the lower lobe, suggesting a metastasis.

*Spleen.*—Weighs 180 gm.  $12 \times 8 \times 4\frac{1}{2}$ . Consistency moderately increased, the organ apparently swollen. The capsule stretched. The nodules are fairly prominent on medulla and lateral borders. On section a rather firm, red surface presents, in which many small gray, Malpighian bodies are seen. The trabeculae increased moderately in number and slightly in thickness. The larger splenic vessels somewhat more prominent than normal. No areas suggesting metastases seen.

*Liver.*—Weighs 1,300 gm.  $24 \times 18 \times 7$ . The consistency moderately less than normal. The surface quite smooth. In it can be seen many roughly circular gray, translucent areas of different size. The capsule thin, the edge soft, thin. On section a somewhat greasy, yellow brown surface presents, in which are many circular, gray, translucent areas, with circumference varying in size from 1 mm. to 6 cm. The lobulations of the liver fairly distinct, fairly regular; the lobules of good size. The vessels and ducts show no abnormality. The gall bladder moderately distended with viscid, greenish black bile. The mucosa thin.

*Pancreas.*—Average size. The consistency in general is somewhat lessened. In the region of the tail, however, there are firm gray, translucent lymph glands and firm gray, translucent tissue, apparently extending between the pancreatic lobules. In general the lobules are small, close together, greasy, yellow in appearance. The islands are made out distinctly.

*Adrenals.*—The right shows marked post-mortem digestion of medulla and portion of cortex. The left is of average size, shows slight digestion of medulla, the cortex is a uniformly brown instead of yellow color.

*Kidneys.*—Together weigh 280 gm. The right measures  $12 \times 5\frac{3}{4} \times 3\frac{1}{2}$ . The left  $11 \times 6 \times 3\frac{1}{2}$ . The cortex slightly uniformly adherent. The surface quite smooth. On section the cortex is fairly regular in width, average 5–6 mm. The striations not apparently distinct, but apparently regular. The glomeruli are not prominent. The tubular parenchyma greasy, yellow, opaque. The medullary portions show nothing abnormal. The pelvis not dilated. The mucous membrane pale. The ureters of average circumference, the membrane pale.

*Pelvic Organs.*—The *bladder* slightly dilated, the mucous membrane pale, some injection of the urethra. The *vagina* shows moderate diffuse thickening of the mucosa. The internal lip of the cervix is smooth, the *outer lobe* fused with the vaginal vault. The uterus is slightly enlarged, the musculature of average thickness. Below the serosa of the fundus, at the right side, there is a large, firm nodule with smooth surface, somewhat larger than a walnut in size. On section had a gray translucent to opaque surface, the tissue arranged in whorls. On opening the uterus, the greater portion of the cavity is filled by a walnut-sized nodule; smooth, firm, spherical, covered by normal looking endometrium. On section this nodule is of an unusual appearance: in great part it is similar to the subserous nodules, but in one portion the tissue is softer, slightly yellow in color and sharply marked off from the remainder of the tumor, the edge of demarcation, however, is irregular. This portion of the mass has a diameter of about 12 mm. There is a hazelnut sized area quite like this latter tissue below the serosa near the cervix. The tubes and ovaries show no abnormalities. The rectum 15 cm. in circumference. The mucosa smooth, in one place there is a small recent hemorrhage or post-mortem extravasation.

*Vessels.*—Dissection of the inferior vena cava and larger branches shows nothing unusual. *Aorta* thin walled throughout, elasticity fair. There are a few scattered small, soft, yellow opaque patches in the intima.

*Neck Organs.*—One of the bronchial lymph glands found moderately enlarged, gray, translucent in appearance. The thyroid is considerably enlarged, each loop bifurcated. On section sharply circumscribed areas containing translucent to brown to greenish colloid material, varying in size from a pea to hazelnut are seen in each lobe. The remainder of the skin has a pale brown appearance. The *trachea* and *larynx* show nothing abnormal. The *tonsils* small, scarred, each shows a few crypts which are filled with purulent and chalky white material.

*Alimentary Tract.*—The *tongue* average size. The *papilla* not prominent. The *esophagus* shows no abnormalities. The *stomach* of average size and thickness, the mucosa shows considerable digestion.

*Brain.*—Weighs 1,350 gm. Shows no definite abnormalities externally.

*Cord.*—Shows no apparent abnormalities.

*Bones.*—The calvarium when held up to the light shows numerous areas of apparent thickening. On sawing through a few of these nothing suggestive of metastases was found. The vertebræ, lower thoracic and upper lumbar, very friable, almost crumbled under saw. The body of the twelfth dorsal vertebra almost entirely gone. The disc above and below it are separated from each other by only a few mm. The sixth rib on the left side fractured at a point of greatest curvature. The right femur diaphysis shows an increased amount of compact bone except the upper portion, where in places the bone of the shaft is somewhat thin, the marrow apparently fairly active, fleshy red and greasy yellow. In addition, the upper portion shows a few discrete firm, grayish yellow nodules, grape seed to pea size, apparently metastases. In the upper shaft, neck and head cancellous bone in places is increased in amount. The bone in the neck and head has a grayish appearance. The neck of the right femur much more friable than normal. (Broken through on removing it from the body.) The left femur on section in general quite similar in appearance to the right; the neck, however, not so friable.

Microscopical examination of the bone of the vertebræ shows an infiltration with carcinoma tissue.

CASE VI. Mrs. D. L. Age 40 years. Present history dates back 14 months, when the patient noticed a hard painless mass in the lower and medium portion of the right breast. She was operated upon at Mount Sinai Hospital six months ago.

On leaving the hospital the patient felt perfectly well for 2 weeks, when she began to experience pain for the first time. This pain was situated in the region of the lower lumbar vertebræ, the patient claiming that the pain was similar to that felt during child birth. The above has persisted ever since. With the onset of pain there developed loss of weight and general weakness. The pain was so severe that the patient has been confined to bed ever since.

The patient was admitted to the Montefiore Home and Hospital on November 10, 1915, her complaints on admission being lancinating pain in the region of the lower lumbar vertebræ and anterior aspect of thigh, loss of weight, general weakness.

The examination of the patient on admission showed the following condition. Right side of chest wall presents a comparatively recent scar of breast amputation. No nodules of subsequent recurrence can be felt along this course.

Axillary and supra-clavicular regions free from palpable glands.

Head of right humerus is painful on pressure. Percussion of anterior surface of chest wall shows no dullness anywhere. Liver does not seem to be enlarged on percussion and is not palpable.

Left lower extremity is bent slightly on account of painful rigidity of flexor muscles. Right lower extremity is freely movable. Upper fourth of right femur is somewhat painful. Same condition exists in upper fourth of left femur.



December 8, 1915, pain at the region of the sacral bone diminished. The patient is generally better able to move around than previously.

February 7, 1916, there seems to be localized pain on pressure over the spinous process of the last lumbar vertebra and over the surface of the upper third of the sacral bone. There appears an edema in both lower extremities after walking.

March 15, 1916, X-ray examination. *Lumbar Spine*.—Slight destruction of the contiguous portions of the second and third lumbar vertebræ with some bone condensation and very marked new bone formation in form of bridge formation on both sides.

The patient is still under observation and is under treatment by X-rays both in the region of the chest and over the region of the second and third lumbar vertebræ, in which the X-ray examination showed with great probability a metastasis in the vertebræ.

At present the condition of the patient is greatly improved, and she walks around freely. A later X-ray examination showed an increase in the bone formation in the region of the second and third vertebræ.

#### DISCUSSION

The experimental and pathological study of the metastatic tumors of the central nervous system, as was shown above, presents many points of theoretical interest. The investigations on the subject may be helpful in the elucidation of the complex phenomena of the interrelation between the development of a malignant tumor and the soil in which it grows.

The practical value on the other hand of the clinical reports of the cases of metastases of malignant tumors in the central nervous system consists in the aid they may offer in the recognition of the cases, as they present themselves to the clinician.

The fact that these metastases occur very rarely is in itself an important reason for the frequent failure of the clinicians to make an early diagnosis.

There are two more factors which increase the difficulties.

In the first place metastasis in the central nervous system may give no clinical symptoms during its entire course. It is even probable that those cases which ultimately develop severe clinical symptoms may have existed for a certain time without causing any manifestations attributable to the nervous system. The reason for it is the following.

Benign tumors of the brain are encapsulated and during their growth compress the brain, increase the intracranial pressure and therefore produce early symptoms. Carcinoma and sarcoma grow invasively and destroy brain tissue during their growth and consequently the combined amount of tissue inside of the skull does not

change and therefore no symptoms manifest themselves until a vital portion of the brain is destroyed (Fig. 9).

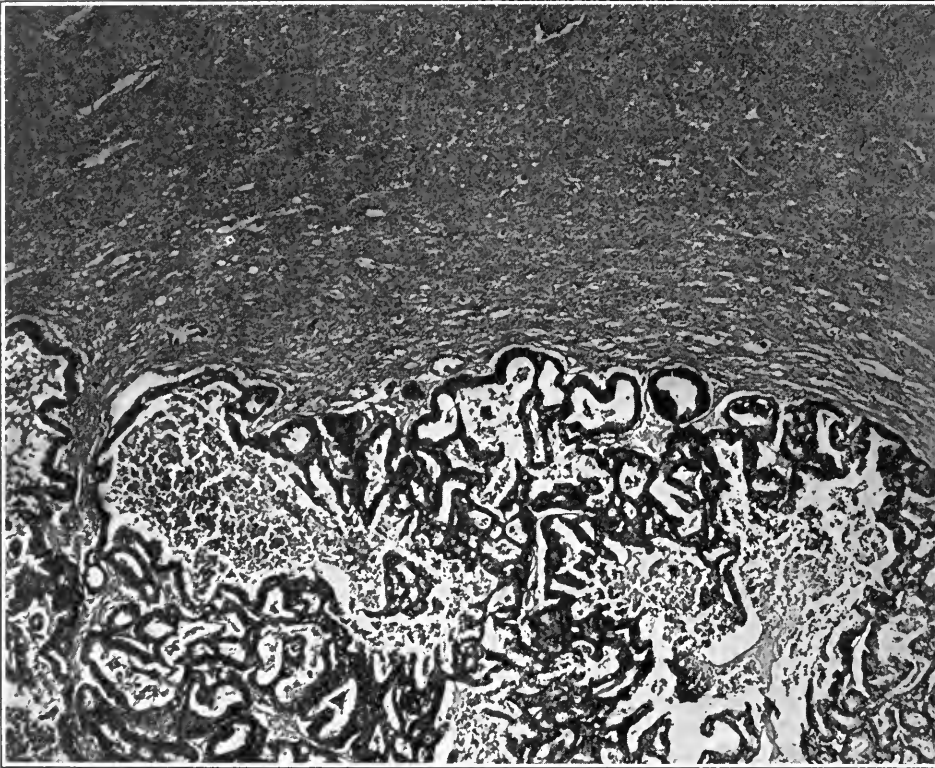


FIG. 9. Adenocarcinoma of the brain, metastatic, showing invasive growth. Microphotograph, low power.

The second and by far the more important handicap to the correct diagnosis of a metastasis in the central nervous system is presented by the fact that the primary tumors may be so insignificant in comparison with the condition in the central nervous system that they escape recognition. In other cases the primary condition, though easy of recognition, may simply have been lost sight of by the clinician. As a result of all this, a faulty diagnosis may be made, and incorrect methods of treatment instituted. A case recently reported by S. H. Brown (19) is characteristic in this respect. The patient suffered from a primary carcinoma of the sigmoid. An exploratory laparotomy was performed on May, 1913. From December 8, 1913, to June, 1914, the patient was given X-ray treatment.

At the end of the year there developed a trophic ulcer of the cornea and severe pain in the region of the trigeminus. On December 7, 1914, an operation for the removal of the Gasserian ganglion was performed. The metastatic carcinoma of the brain was only recognized post mortem. It would seem that in this case the operation for the removal of the Gasserian ganglion was too severe, and large doses of morphine should have been the method of choice.

In metastases of carcinoma of the spine the primary malignant tumor escapes notice even more frequently. Case IV presents such an instance. The primary carcinoma of the lungs gave no clinical symptoms. The paraplegia was considered to be the primary disease and was thought to have been caused by a trauma of the spine. It would seem that in this, as well as in many other similar cases, an X-ray examination could have cleared up the diagnosis. The application of a plaster cast for five months for a metastasis of carcinoma of the spine was also a useless procedure.

Another case of a primary carcinoma of the thyroid with a metastasis in the spine, which was admitted to the Montefiore Home and Hospital, and in which faulty methods of treatment were applied and the correct diagnosis made late in the course of the disease, will be reported in detail later.

Very little can be said in regard to the *therapy* of this condition. In view of the invasive growth described above, surgical interference is quite out of question. Very recently, Küpferle and Szili (20) described a case of carcinoma of hypophysis greatly improved under the influence of X-ray therapy. Their patient was operated upon and his condition improved for a time, then the growth recurred and the patient became totally blind. X-ray treatment was instituted, the vision improved and this improvement lasted until the report was published ten months later.

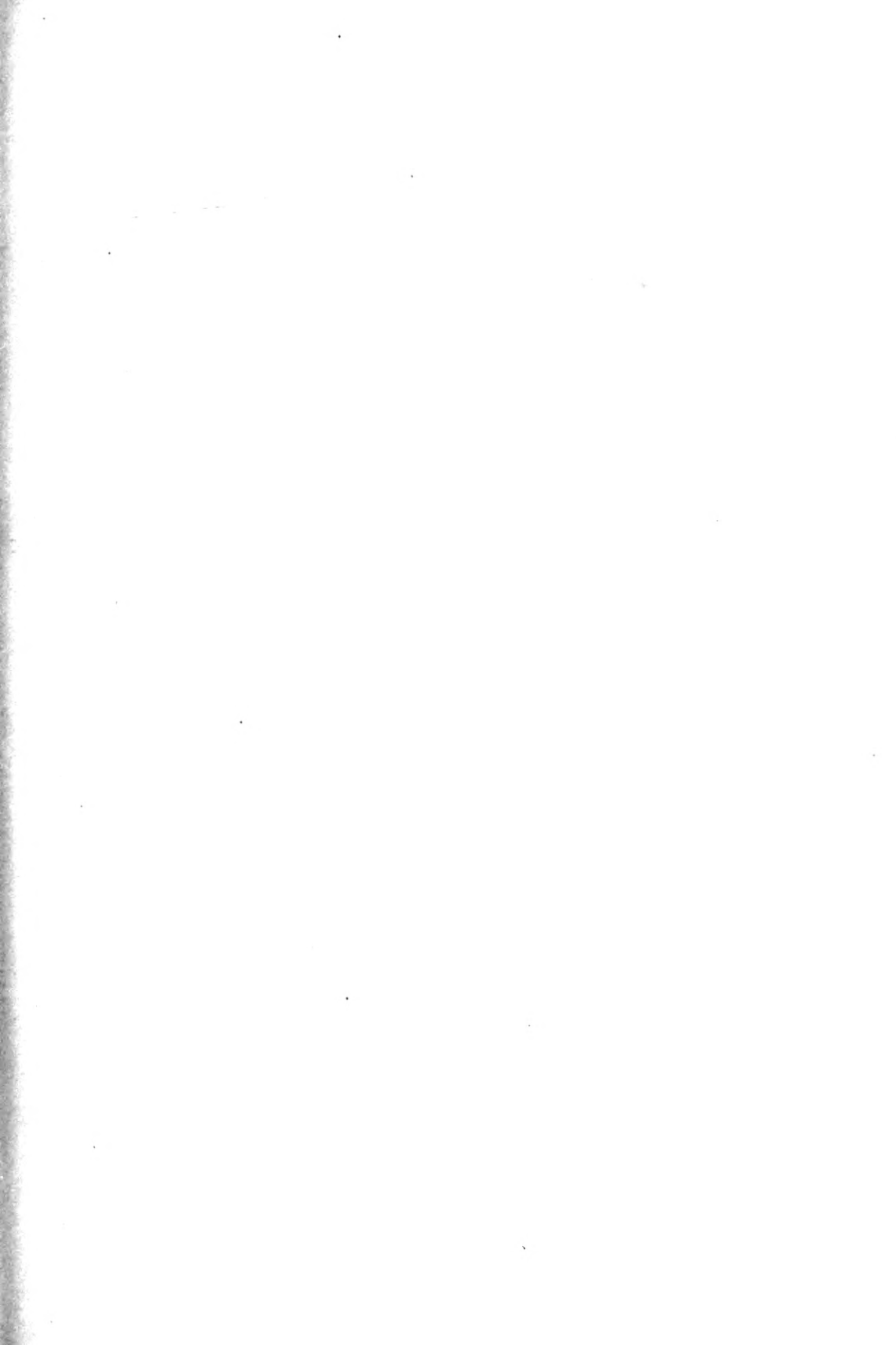
The condition of the spine in the Case VI reported here was also apparently favorably influenced by X-ray therapy, though it is too early to draw any definite conclusions. Pfahler (21) and the writer (22) reported cases recently in which metastases of carcinoma in the ribs were benefited by X-ray therapy. In a word, the fact that metastasis of the central nervous system is encased in a bone does not interfere with the action of the X-rays, and it appears probable that when the diagnosis is made sufficiently early, distinct benefit may be obtained by this method of treatment.

The very important *conclusion* to be drawn from the analysis of the clinical cases of metastasis of carcinoma in the central nervous system is that the clinician must keep in mind the probability of

cancer just as steadily as of syphilis or of tuberculosis. As a result, there will follow a better coöperation of the specialties concerned in the subject and as a consequence a more prompt diagnosis and more efficient methods of treatment.

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# THE RATIONALE OF RADIUM THERAPY IN CANCER\*

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NEW YORK CITY.

## THE SPECIFICITY OF THE BIOLOGICAL ACTION OF RADIUM.

THE terms "selective action" and "selective absorption" are being employed more or less promiscuously in defining the peculiar influence which the *x*-rays and radium exert on plant and animal cells. In reality, the two terms imply different phenomena in the interaction between the rays and the cells.

The fact is well established that the biological effect of the rays on plant and vertebrate animal organisms differ within the various tissues. While the spermatozoa-forming epithelium and the Graafian follicles, for instance, are extremely sensitive to the rays, nerve tissue and the structures of the eye are highly resistant.

The cells most sensitive to the action of radium and *x*-ray are the leukocytes, and these cells present the most favorable material for the study of the "selective action" of the rays.

In a case of lymphatic leukemia with an initial leukocyte count of 226000, an enlarged spleen without any enlargement of the lymph glands, the writer made two applications of radium to the spleen within a week, 2016 millicurie-hours in all. The leukocyte count came down to 12000 and the spleen diminished to a half of the original size.

Figures 1 and 2 show the blood pictures before and after radium applications to the spleen of another case of lymphatic leukemia. In this case there were large lymph glands in the axilla and the spleen reached below the umbilicus. After radium treatment the spleen and glands diminished in size and the leukocyte count went down from 180000 to 50000.

This rapid destruction of a specialized tissue by an external application of radium to the spleen which was not followed by even an erythema of the skin in the field of application, presents a remarkable biological phenomenon indeed.

The "selective" biological action of radium goes beyond the apparent structural differences of the cells. The lymphocytes of lymphatic leukemia and those of conditions of inflammatory leukocytosis are morphologically identical. None the less, radium destroys rapidly the former and has a comparatively slight effect on the latter. The same difference may be noted, for instance, between a lymphosarcoma of a lymph gland and a tubercular lymphoma. The latter condition is influenced by radium with much greater difficulty than the former.

Another proof of the remarkably fine adjustment of the "specific action" of the rays on cells was obtained by the writer in the course of a study of the blood of cases of skeletal metastases of carcinoma treated with radiations.

Radium and *x*-rays reduce rapidly the number of myelocytes in the blood of cases of myelogenous leukemia. The blood of cases of skeletal metastases of carcinoma also frequently contains an increased number of myelocytes in the blood. These latter myelocytes are not influenced by the rays, though they are morphologically identical with the myelocytes in myelogenous leukemia. The explanation of this phenomenon lies in the fact that the two types of myelocytes differ biologically. The myelocytes in myelogenous leukemia, as well as the lymphocytes in lymphatic leukemia, are analogous to cancer cells. They are young, rapidly proliferating cells and therefore highly sensitive to the rays. The lymphocytes in inflamma-

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tory leukocytosis and the myelocytes in the blood of skeletal metastases are more mature cells; they do not proliferate so rapidly and are therefore more resistant to the rays. Thus the term "selective action," means that *the identical rays act differently on different tissues.*

On the other hand, there is ample clinical

from over 95 per cent to as little as 16 per cent.

In a second series of experiments, two turtles were superimposed and both animals rayed in the same manner as in the first series of experiments. In the upper turtle of this series, the reduction in the number of lymphocytes was as great as in the first ser-

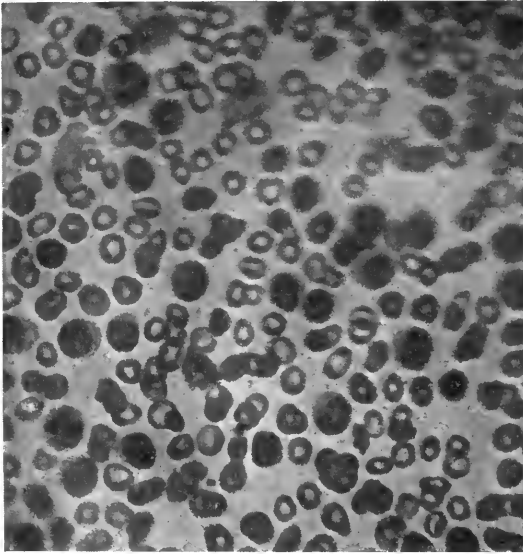


FIG. 1. MICROPHOTOGRAPH. BLOOD SMEAR OF LYMPHATIC LEUKEMIA BEFORE TREATMENT.

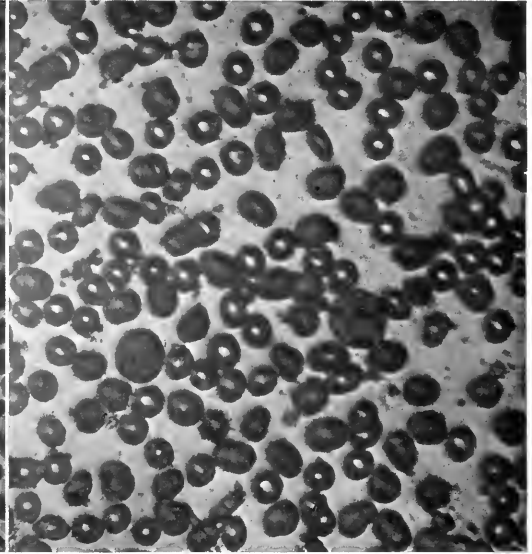


FIG. 2. MICROPHOTOGRAPH. BLOOD SMEAR OF LEUKEMIA AFTER TREATMENT.

evidence of the fact that rays of a different quality affect differently the same type of tissue. For instance, soft  $x$ -rays and alpha rays of radium act differently on the skin from the hard  $x$ -rays and the gamma rays of radium. Experimental evidence of the existence of this difference was obtained by the writer in a study conducted in collaboration with M. Levine.<sup>1</sup>

The investigation consisted in the study of the influence of the  $x$ -rays on the lymphocytes of a turtle. This animal was selected because it has comparatively little of skeleton and bone marrow, and as a result the main type of white cells in the blood are the lymphocytes. Very large doses of unfiltered  $x$ -rays were employed, and the whole body of the turtle was subjected to the rays. Differential blood count after treatment showed that the number of lymphocytes was reduced

ies of experiments, while the reduction in the lower animal was much less pronounced and always remained above 50 per cent.

In a third series of experiments, a dead turtle or a layer of meat was placed over the living turtle and the whole  $x$ -rayed. In this series of experiments, the only live turtle used was at the same distance and in the same relative position to the rays as the lower turtle in the second series. Since the general absorption of  $x$ -rays and rays of radium takes place in the same degree, whether the rays pass through a living organism, inorganic matter or water, then the only live turtle in the third series of experiments did not receive a greater fraction of the whole amount of general radiation than the lower turtle in the second series; but the percentage of destroyed lymphocytes was the same as in the upper turtle of the second series. The ex-

planation of this phenomenon is as follows: The particular type of rays which is affecting the lymphocytes of the upper turtle became itself destroyed or "absorbed" in the course of its activity, and there was left a smaller quantity of this type of rays to act on the lower turtle; while in the third series the meat of the dead turtle did not contain any living lymphocytes which could "absorb" the special type of rays, and the whole amount acted on the live turtle which lay under the dead animal.

Variations in absorption of different types of rays have been shown by physical research to be true for metals, and the same is evidently also true for living tissues. Thus in contradistinction to "selective action" the term "selective absorption" means that *the same tissue may destroy or "absorb" one type of rays and not influence another.*

#### THE SIGNIFICANCE OF "SELECTIVE ACTION" OF THE RAYS IN THERAPY.

Both the phenomena of "selective biological action" and of "selective absorption" are of great importance for the estimation of the therapeutic value of the rays. The true valuation of the "selective absorption" cannot be obtained until a great deal more research shall have been undertaken as regards the best types of the rays, methods of filtration and correct distance to be applied in therapy. It is fairly well established, however, that the harder rays have a more selective action on the tissues than the softer rays. It is therefore self-evident that the action of radium must be different qualitatively from the x-rays and must be more beneficial for therapy.

The "selective action" of the identical type of rays on various tissues is a phenomenon of the greatest importance in therapy and places ray treatment on an equality with true specific methods of treatment, like salvarsan, mercury or quinine.

Furthermore the adjustment is even finer in ray therapy than in chemotherapy. The chemical substances in the latter methods of therapy act on parasites which differ

to a greater extent from the body cells of the host than do the tumor cells from the normal tissue cells.

The great practical value of this "selective action" of the rays consists in the fact that large quantities necessary for the treatment of malignant tumors may be employed without injuring the adjacent normal tissues. The following case indicates how well normal tissues may resist large quantities of radium sufficient to influence a malignant tumor, when the rays are correctly filtered and applied at a proper distance.

Miss L. M., forty-three years old, single. Patient had right breast removed for carcinoma July, 1918. In June, 1919, she began to experience pain in right hip, which at first was intermittent, and from December, 1919, constant. X-ray examination showed metastasis in the head of the femur. About the middle of November, 1919, patient developed esophoria of the left eye. Ophthalmoscopic examination made in December, 1919, revealed the following condition:

Disc color normal, surface flat; no elevation or depressions. Arteries and veins normal in caliber. Peri-papillary area normal. Macular area free from any pathological process. At the upper and inner quadrant of the disc vessels appear to be blurred and can be distinctly seen with the 7D lens. From this area and extending to the periphery one sees apparently a protruding mass, globular in outline, with a complete ill-defined margin. Color of the mass slightly grayish, its surface shows lighter areas, apparently no elevations or depressions on the mass. No detachment of retina apparent, also no evidence of any hemorrhage or exudation in the fundus.

*Diagnosis:* Metastatic tumor of the retina.

On the same day treatments were begun and the following quantities were given.

Dec. 9, 1919	83.4 millicuries applied for 5 hours.
Dec. 12, 1919	93.7 millicuries applied for 6 hours.
Jan. 7, 1920	47.4 millicuries applied for 8 hours.
Jan. 28, 1920	67. millicuries applied for 10 hours.
Feb. 7, 1920	66.7 millicuries applied for 6 hours.
Feb. 28, 1920	68. millicuries applied for 10 hours.
Mar. 13, 1920	61.1 millicuries applied for 12 hours.

At the last examination which was done in August, 1920, the area of the tumor on the retina was found to be less prominent, being only two to three D diameters elevation and passing more diffusely into the retinal structure. Apparently in the eight months since the first examination the tumor, if anything, diminished in size, and what is of greater importance, all the other

cells consisting in vacuolation of the protoplasm, pycnosis of nuclei, karyolysis, and ultimately complete necrosis of the cell. The cellular changes are accompanied by a round-cell infiltration, which is subsequently changed into dense sclerotic connective tissue, poor in blood vessels. This new connective tissue formation ultimately dominates the picture to such an extent that some



FIG. 3. TO THE LEFT AN INOCULATED AND X-RAYED PLANT, showing at *b* a minute swelling at the point of inoculation. TO THE RIGHT AN INOCULATED CONTROL PLANT showing at *c* a fully developed crown gall. The plants themselves show no abnormality.

tissues of the eye remained normal. In this case quantities of radium were applied to the eye sufficient to influence a large carcinoma mass, and neither the skin of the eyelid, the conjunctiva nor any of the tissues of the eyeball were impaired in any way.

#### THE MECHANISM OF THE ACTION OF RADIUM ON CANCER

The fact that radium may destroy a malignant tumor without injuring the adjacent normal tissues is a true indication that radium does not act as a caustic but has a specific "selective action" on the tumor. What is the actual mechanism of this action? The microscopic analysis of cancer tissue submitted to radiation most generally shows marked degenerative changes in the tumor

observers maintain it is the only direct effect of radiation, while the destruction of the tumor cells is secondary and due to lack of nutrition.

In order to ascertain whether the rays have a direct effect on the tumor cells, the writer has undertaken in association with M. Levine,<sup>2</sup> a study on the influence of  $x$ -rays on the crown gall. This disease is a new growth which develops spontaneously or may be induced artificially in various plants. It presents an ideal subject for the study of the direct influence of the rays on the tumor cells, since plants do not possess any lymphoid tissue. As a result, no connective tissue forms, and the behavior of the tumor cells can be studied unobstructed. The results of this investigation show that the rays arrest the development of the tumor. While in all

the untreated control plants, there developed a large crown gall, the majority of the x-rayed plants did not develop any growth, and only a slight swelling appeared at the place of inoculation. (Figure 3 shows a

of the rays, but takes place in the natural course of the life cycle of the cancer cell. This cycle consists of *youth*, or period of development; *maturity*, or period of function; and *senility*, or period of degeneration, which gradually leads to death. In parenchymatous organs, like the liver and kidney, the first period is usually completed during embryonic life or at very early age; the second period continues through the whole life of the organism, and the third period is attained at the old age of the organism or near its death.

The life of an individual cancer cell, on the other hand, is very short; it changes rapidly from an embryonic into an adult and then immediately into an aged, degenerated cell, and this process takes place continually, irrespective of any extrinsic aid. But in a malignant tumor the majority of the cancer cells are quickly rejuvenated before they reach senility through the fact that each cancer cell divides into two young daughter cells. When the rays arrest this proliferation, then the cancer cells, without any further



FIG. 4. AN INOCULATED AND X-RAYED PLANT, shows at *b* a stunted crown gall.

treated plant and a control.) In a few plants there developed a small stunted growth. (Fig. 4.)

The microscopical study of the radiated plants revealed a very instructive condition. Not only the stunted growths but even the minute swellings which on inspection were thought by the writer to be scars caused by the mechanical injury of the needle prick, showed the presence of morphologically unchanged crown gall cells. Figure 5 shows a fully developed crown gall, and Figure 6 shows a small group of crown gall cells in a minute swelling of a petiole (the stem of a leaf). This investigation as well as the clinical and pathological studies of the writer indicate that the first effect of the rays is exerted directly on the tumor cells. This effect consists in the inhibition of the proliferating power, in the *sterilization*, as it were, of the cancer cells. The degeneration and destruction of the cancer cells and the formation of the sclerotic connective tissue take place subsequently through the action of the rays; moreover this cell degeneration and cell death may not be due directly to the action



FIG. 5. MICROPHOTOGRAPH CROWN GALL *a* shows tumor cells, *b* normal stem cells

outside aid, mature and degenerate. It is interesting to note in this connection that the life of the epithelium of the skin or testicle is nearly as short as one of the malignant tumors, and the rays act on these organs as specifically as they do on malignant tumors. Thus the inhibition of the proliferating power of the cancer cell and its ultimate degeneration and death constitute the primary and main action of the rays on a malignant tumor.

The round cell infiltration, which surrounds the groups of radiated cancer cells and which is subsequently changed into dense sclerotic connective tissue, is of secondary occurrence, though for practical purposes it is of greater importance than the destruction of the cancer cells themselves. The importance of the connective tissue consists in the following. After the most perfect results of radiation, there may remain a certain number of viable though stunted cancer cells; the dense connective tissue wall surrounds these cells and keeps them in check.

#### THE RÔLE OF THE NEWLY FORMED CONNECTIVE TISSUE.

The formation of the connective tissue around the rayed cancer cells is not due to the direct influence of the radiations, and raying of other conditions like thyroid gland, cheloid, etc., is not followed either by cell infiltration or by connective tissue formation.

The experimental investigations of the writer<sup>3</sup> indicate that this connective tissue formation may represent an attempt by the organism to protect itself against the further growth of the cancer by walling it off from the normal tissues by a connective tissue barrier.

In a series of experiments on inoculable cancers of the white rat, the writer has shown that when particles of the tumors were inoculated into internal organs (liver, kidney, brain, testicle and so on) of susceptible animals, the tumor grew diffusely, invaded the normal tissues of the organ, and

there was no connective tissue formed around the graft. Furthermore the adjacent normal tissues became diseased<sup>4</sup> (fatty degeneration) under the influence of the grow-

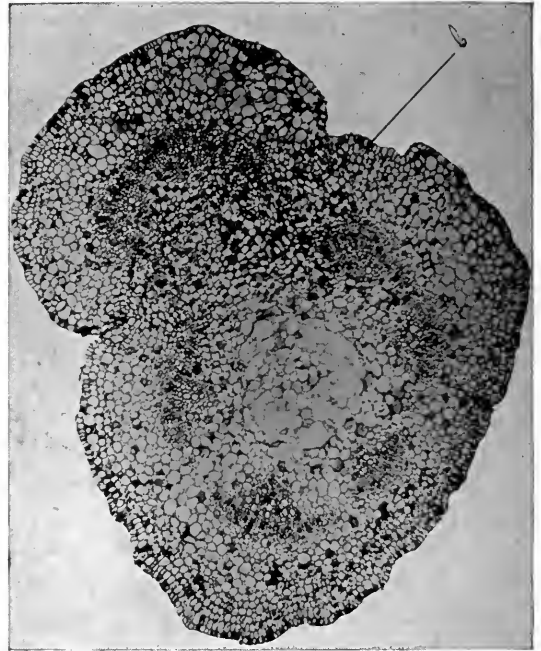


FIG. 6. MICROPHOTOGRAPH. CROSS SECTION OF A PETIOLE. Shows at *b* a small group of tumor cells.

ing tumor before they were invaded by the latter.

In another series, the animals were made by a preliminary treatment resistant to the growth of the tumor, and then particles of the tumor were inoculated into internal organs. In these animals the grafted cancer tissue did not grow but was surrounded by newly formed connective tissue. Thus it appears that when the cancer cells are malignant and proliferate they also interfere with the formation of the connective tissue wall. When the animal is resistant it inhibits the proliferation of the cancer cells and creates at the same time a connective tissue barrier. A similar mechanism most likely takes place in the course of the raying of cancer tissue. The rays inhibit the proliferating power of the cancer cells and destroy their malignancy. The organism is then enabled to form

a protective connective tissue barrier around the tumor.

That this conception is plausible may be gathered from the fact that a number of

form with greater precision and by far greater frequency what the organism itself attempts to do haltingly and in rare instances.

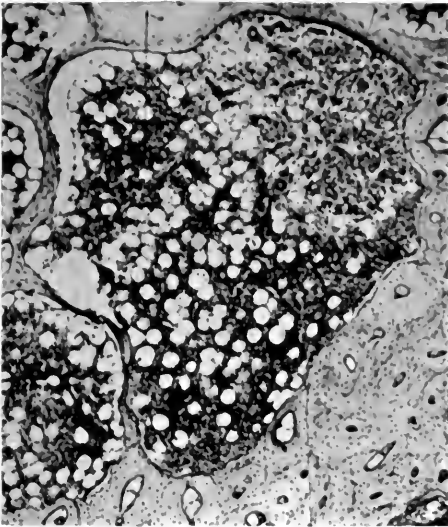


FIG. 7. MICROPHOTOGRAPH. MINUTE NODULE OF CARCINOMA IN THE BONE MARROW. *a* shows carcinoma; *b* normal marrow.

pathologists (Borst,<sup>5</sup> Schmidt,<sup>6</sup> Orth<sup>7</sup>) describe the same phenomenon as occurring spontaneously in the human. A connective tissue stroma surrounds a group of cancer cells, gradually increases in size, compresses



FIG. 8. MICROPHOTOGRAPH. SHOWS A GREAT DEAL OF NEW BONE FORMATION IN THE VICINITY OF AN OLD BRIDGE OF COMPACT BONE TISSUE. *b* shows old bone; *a* new bone.

the cancer cells and produces a local cure of the growth.

In other words radium and the x-rays per-

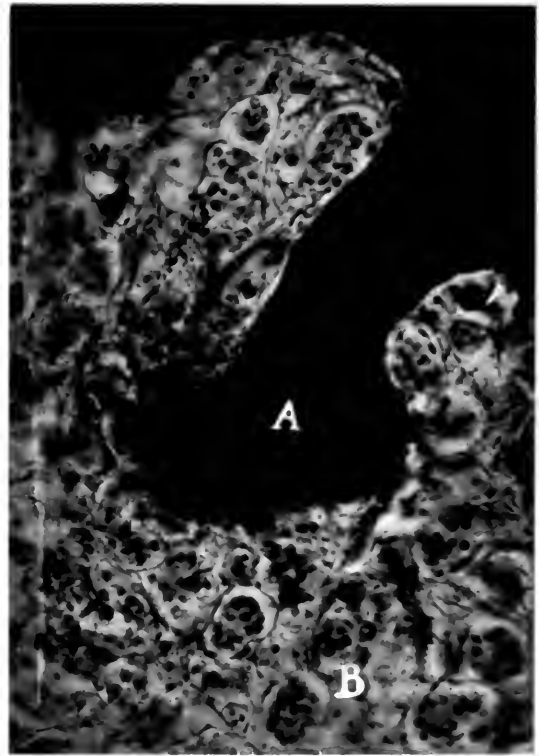


FIG. 9. MICROPHOTOGRAPH. TWO BONE LACUNAE FILLED WITH CARCINOMA CELLS. Low magnification. *A* shows bone; *B* carcinoma.

#### ACTION OF RADIUM ON MALIGNANT TUMORS OF THE SKELETON.

The mechanism of the action of the rays on malignant tumors, the sequence of events as well as the fact that results obtained through this action resemble the phenomena which occur spontaneously in the organism, can be demonstrated most clearly in the study of the influence which radium exerts on carcinoma and sarcoma of the skeleton.

In a pathological study of skeletal metastases of carcinoma, the writer<sup>8</sup> has shown that the metastasis usually begins its development within the marrow, and when the nodule of carcinoma is small, the surrounding bone-marrow appears quite normal (Fig. 7). As the tumor nodule increases in size, it



approaches and invades the compact osseous tissue or the compact osseous partitions of the cancellated bone. Then there begin to appear characteristic changes in the bone tis-

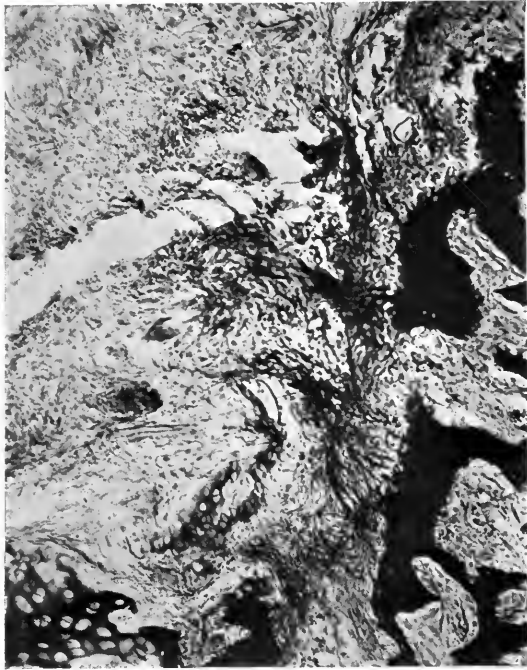


FIG. 10. MICROPHOTOGRAPH. MICROSCOPIC SECTION OF A SKELETAL METASTASIS STAINED WITH VAN GIESON. Shows Collagen fibrils emerging from the old bone and uniting with other fibrils.

sue. These changes are of two types, *osteoplastic*, in which extensive new bone formation takes place around the metastatic tumor, and *osteoporotic*, in which the changes consist in destruction of the compact bone. The studies of the writer have shown that both conditions are usually present. Figure 8 shows an extensive new bone formation, and Figure 9 shows only destruction of the old bone, and both specimens were obtained from different regions of the same metastatic tumor. The destruction of the old bone is caused mainly by the cancer cells themselves acting as osteoclasts, as is clearly seen in Figure 9. Figure 10 shows collagen fibrils formed from the old bone. These fibrils gradually unite in thick bundles and subsequently form new bone.

Most frequently the metastatic nodule in-

creases in size, suppresses the power of the organism to create new bone and progressively destroys the old bone. The spontaneous healing power of the organism is thus quite imperfect and comes into play very rarely indeed. In a previous communication the writer<sup>9</sup> has shown that radium therapy may enhance the healing power of the organism, destroy at least a major part of the malignant tumor, and surround it with newly formed bone. Further progress of this study may be reported here. The three cases reported in the previous publication are well to-day, six, five and a half, and five years respectively since the beginning of the treatment. Figure 11 shows the roentgenogram of one of the three cases five years since the beginning of the treatment. The metastasis in the spine—second and third lumbar vertebra—became manifest six months after a radical amputation of the breast. In November, 1915, the patient entered Montefiore Hospital, suffering from paraplegia dolorosa. At present the patient is clinically well.



FIG. 11. ROENTGENOGRAM. METASTASIS OF CARCINOMA IN THE SECOND AND THIRD LUMBAR VERTEBRA FIVE YEARS AFTER TREATMENT.



The roentgenogram taken in August, 1920, shows a good deal of new bone formation in comparison with the findings five years ago.

Figures 12 and 13 present two roentgenograms of the right clavicle of a boy seven-



FIG. 12. ROENTGENOGRAM. SARCOMA OF CLAVICLE.

teen years old who suffered from multiple sarcomata of the skeleton with metastasis in the lungs to which the patient succumbed. Radium was applied experimentally to the tumor of the clavicle. Figure 13 shows clearly that the tumor of the soft tissue disappeared, and a great deal of new bone was formed.

Figures 14 and 15 present roentgenograms of the spine of a woman twenty-seven years of age whose right breast was removed for carcinoma in November, 1918. A year later there developed a paraplegia dolorosa, the patient entered the Lenox Hill Hospital, roentgen examination showed destruction of bone of the fifth lumbar vertebra. On January 21, 1920, the first radium application to the affected bone was given. In August, 1920, seven months later, a roentgenogram (Fig. 15) was taken and it shows a good deal of new bone formation. At the same time the clinical condition of the patient is greatly improved.

#### THE ADVANTAGES OF THE USE OF BURIED EMANATION TUBES.

The data furnished in this paper indicate that radium exerts a truly specific selective

action on cancer tissue. Biologically, then, radium therapy in cancer has a thoroughly scientific foundation and presents the nearest approach to a specific therapeutic measure against the disease. In practice, however, the action of radium has its limitations, and the results obtained thus far vary in accordance with the size and location of the tumor. The effectiveness of the rays diminishes in inverse ratio to the increase of the distance and the size of the tumor. A preliminary surgical removal of the main mass of the tumor, even when radical surgery is impossible, diminishes the difficulties in connection with the size of the tumor. The placing of the radium in near approximation to or within the tumor does away with the disadvantages which are presented by a greater distance between the source of radiation and the tumor.



FIG. 13. ROENTGENOGRAM. SARCOMA OF CLAVICLE AFTER APPLICATION OF RADIUM SHOWS NEW BONE FORMATION.

A new method was recently developed by Duane of Boston which obviates to a great extent the difficulties created both by the size and location of the tumor. It consists in the use of buried radium emanation tubes.

Each minute glass tube contains not more than about 3 millicuries. A sufficient number of the tubes is buried in the tumor to cover its whole mass and is left there permanently. The emanation decays after a time and the tubes become inert.

While this method is simpler and frequently more efficient than the external ap-

external application of radium in combination with incomplete surgery and become the method of choice in many conditions. The method of buried emanations should always be accompanied, however, by external application in the areas of the regional lymph glands and the areas directly adjoining the tumor.



FIG. 14. ROENTGENOGRAM. METASTASIS OF CARCINOMA OF THE FIFTH LUMBAR VERTEBRA.



FIG. 15. ROENTGENOGRAM. METASTASIS OF CARCINOMA OF THE FIFTH LUMBAR VERTEBRA AFTER APPLICATION OF RADIUM. Shows new bone formation.

plication of radium, one must not lose sight of the fact that the action of the buried emanation is not as strictly selective as the external application of well-filtered rays. The emanation in the minute tubes is filtered only by the glass walls of the latter. Therefore the soft beta rays also act on the tumor and may produce small foci of necrosis around the buried tubes. Care must be taken, therefore, not to place the tubes too near the surface of the tumor nor too near large blood vessels or nerves. Neither must the emanation tubes be placed too near each other. But with correct technique this method will in the near future supersede the

#### THE CORRECT FUNCTION OF RADIUM AND THE $x$ -RAYS IN CANCER THERAPY.

There has developed in some quarters recently a tendency to apply to a cancer patient one intense dose of radium or  $x$ -rays which is not to be followed by another application for a long period of time, if at all. In this manner an attempt is made at a radical cure of the disease.

In the opinion of the writer, this method is erroneous and must be followed by many ultimate failures for this reason: As stated above, the first action of the rays on the cancer cell consists in the inhibition of the *pro-*

*liferating power* of the nucleus. As a result the cancer cell does not divide into two young cells but enters the state of maturity. Such a *matured* cancer cell or a *stunned* cell, as stated above, may remain alive and it is then probably as resistant to the rays as the adjoining normal tissue cells and may not be destroyed by the rays. None the less it is potentially a cancer cell, and it may recover

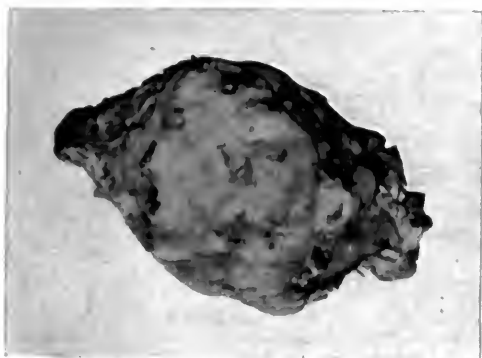


FIG. 16. PHOTOGRAPH OF A RECURRENT NODULE OF CARCINOMA TREATED BY RADIUM. Darker area on the surface presents new carcinoma tissue.

sooner or later its proliferating power and create a new tumor mass if it is not radiated repeatedly. Such a cancer cell in its matured state may appear on superficial analysis as a radio-resistant spore in bacteriology. The whole phenomenon, however, of the temporary resistance of an individual cancer cell to the radiations as explained above is an entirely different condition and must be treated accordingly.

No matter how intensive the radiation, it is just as incapable of destroying in every patient all the cancer cells of the treated region as radical surgery is of curing 100 per cent of the operated cases. Therefore the correct technique consists in repeated applications of a correct dose at stated intervals. The insertion of buried emanation tubes should usually be done only once in the same region; but it must be followed by repeated external applications in the surrounding areas.

The following case illustrates clearly the necessity of repeated applications. The patient developed, subsequent to an amputation

of the right breast for carcinoma, a nodule of recurrence in the infraclavicular region. Several applications of radium were given. The nodule at first diminished somewhat in size and then remained stationary. The patient discontinued treatment, and when she was seen several weeks later the nodule appeared to have increased in size. The nodule was then excised and examined microscopically. The findings were very instructive. Nearest to the skin there was found a thin layer of active carcinoma tissue, while the rest of the nodule throughout its depth consisted of dense connective tissue and did not contain any cancer cells. The only plausible explanation of the appearance of the specimen is as follows: Radium destroyed all the cancer tissue and left behind only a few scattered viable cancer cells in the vicinity. These cells formed a new tumor on the top of the old nodule when the treatment was discontinued. Were the whole layer of active cancer tissue a part of the original nodule then it would



FIG. 17. MICROPHOTOGRAPH Low power. The darkest area on the surface shows new carcinoma tissue.

have been the first to be influenced by radium, since the latter produced a perfect effect on the whole depth of the nodule. This case thus proves conclusively that scattered viable cells may remain uninjured in the path of the rays, even at the surface of the

tumor where the action of the rays was most intense. Hence the necessity of repeated radiations is apparent. Figures 16 and 17 show a gross photograph and a low power microphotograph of the nodule.

Besides the recurrences at the periphery of or at a short distance from the region of the primary tumor the most important cause for the failure of all methods of cancer therapy is the formation of metastases in distant regions of the organism. In the early stages of the disease, these metastatic nodules may be too small to be detected, but they increase in size and virulence while the primary tumor is being treated. The only method at our command to lessen the frequency of these two types of recurrences is to ray prophylactically the regions in which the formation of recurrent or metastatic tumors is probable, and this is in the estimation of the writer the true function of  $x$ -ray therapy in cancer. For the destruction of a discrete circumscribed cancer nodule of a fair size, the action of radium applied by the aid of modern technique and in the large quantities which most of the operators control to-day, is by far superior to the  $x$ -rays. On the other hand the  $x$ -rays should be used when a great deal of ground has to be covered, but where all the nodules are minute or even microscopical. This is the aim of the so-called prophylactic  $x$ -ray treatment of the chest or of parts of the skeleton. All these areas frequently contain disseminated microscopical groups of cancer cells, though there is no clinical evidence of discrete metastases.

#### CONCLUSION

To a casual observer it may appear that the practical therapeutic results obtained by radium in cancer should not warrant the enthusiasm of the radiumtherapeutist. But a closer student in the domain of radiumther-

apy cannot fail to appreciate the fact that radium is the most powerful agent in the whole therapeutic armamentarium of medicine, and that the selective action of the element, when the quantity and quality are correctly adjusted, presents a most remarkable phenomenon. Moreover not all of the failures by far must be ascribed to the inefficiency of the agent. The percentage of cases suitable for radiumtherapy is as small as the number of cases suitable for radical surgery.

Even if radiumtherapy should not have accomplished anything else, it is of great value because it is gradually dissipating the feeling both within the profession and the laity, that a diagnosis of cancer means a death warrant. The association between radium and cancer is also becoming more generally realized. As a result the radiumtherapeutist is being called upon with increased frequency to decide on matters which are purely in the domain of cancer research. It is imperative therefore that every radium worker should become a student of the whole domain of cancer research—biology, pathology, clinical diagnosis, surgical or combined therapy. Each radium establishment which controls large quantities of element, should become a center for cancer research. Both greater success in the results of radiumtherapy in cancer and progress in the knowledge of the whole cancer problem will follow this course of action.

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# CANCER THERAPY\*

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## *The Proper Co-ordination Between Surgery, Radium and the X-Rays*

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THE AIM of any therapeutic measure in medicine is to completely and permanently eradicate the disease. The most efficient method for obtaining such a result is to employ a specific remedy. It is difficult, however, to conceive the existence of a truly specific remedy against cancer. The best evidence gathered from all experimental and clinical research to date tends to the conclusion that cancer is neither an infectious nor a systemic constitutional disease, but manifests itself as a local disturbance in a group of organ cells. It begins its development as a local condition, a transformation of a small group of normal cells of a certain organ into cancer cells. Some of these transformed cells become disassociated from the primary tumor and are transferred to distal regions of the organism where they form secondary metastatic tumors and again act to produce local disturbances.

Even for a distinctly infectious disease like tuber-

culosis the etiology of which is perfectly clear, no specific remedy is as yet discovered. How much more difficult is it to develop a truly specific method of treatment for cancer! Such a therapeutic measure would have to affect deeply the cancer cells and at the same time remain innocuous to the adjacent normal cells of the same organ as well as to all the other normal cells of the organism.

It seems to be characteristic of cancer therapy that each individual worker employing a single therapeutic agent becomes enthusiastic over his immediate results and consequently over his particular remedy. The surgeon, the radium or the X-ray worker recognize the worth of their own work only. Just at the present moment a certain number of German clinicians<sup>1</sup> seem to maintain that the results obtained with X-ray therapy by the aid of the latest machines are superior to those resulting from any other method of treat-

<sup>1</sup> L. Seltz & H. Winiz. *Unsere Methode der Röntgen-Tiefentherapie und ihre Erfolge*. Berlin, 1920.

ment of cancer. This presents a rather unfortunate situation since such an attitude must be followed by disillusionment and resulting pessimism towards important and useful single agents in cancer therapy.

#### *Evaluating Methods*

To date the total results obtained in the treatment of cancer with all the methods at our command are

methods of surgery, of modern radical surgery, as well as of radium and X-ray therapy, and the newest high-voltage technique. As a result of these years of study the writer feels justified in making the following statement: An individual cancer patient has a far greater chance for recovery at present than he had thirty-five years ago. On the other hand, undue enthusiasm over immediate results does only harm to

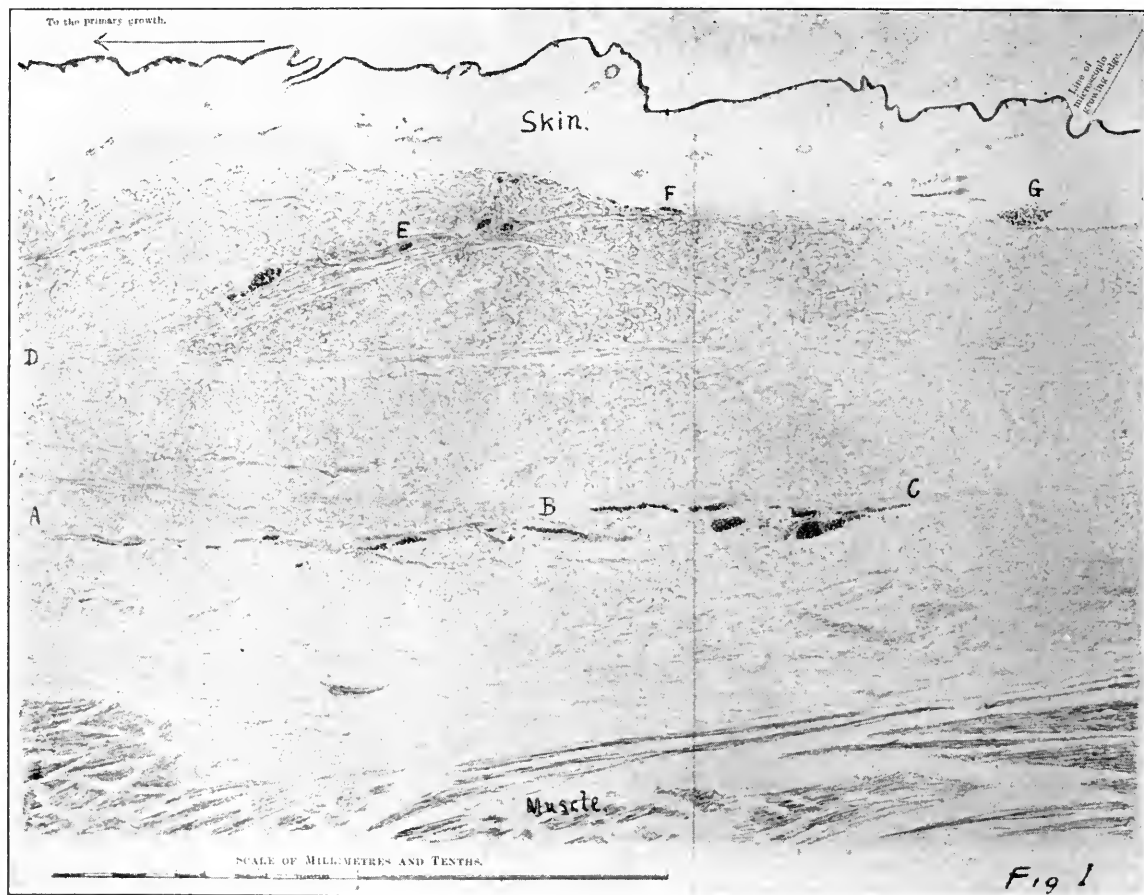


Fig. 1. Permeation of lymph vessels by cancer cells (from W. S. Handley *Cancer of the Breast*).

still limited. It is therefore of the utmost importance not to impede the correct and scientific progress of the subject by either an over-enthusiasm over one method or an unwarranted pessimism over the other. Surgery, radium and X-ray therapy represent to-day the sum total of the methods we possess in combating the disease. The most important problem to-day is to obtain a true evaluation of the three methods of cancer therapy and find a way for their proper co-ordination.

In the years of constant interest and active participation in the development of the subject, the writer had the opportunity to follow the results of the old

the progress of the work, since immediate results must usually be greatly discounted a few years later in cancer therapy.

#### *Surgery in Cancer*

In the course of the last quarter of a century a great deal of progress has been achieved in the surgical treatment of cancer. The so-called radical methods of operative procedure were developed as a result of anatomical studies of the distribution of the lymph channels through which the disease spreads.

An excellent example of such studies is the anatomical and pathological investigations of W. S. Handley<sup>2</sup> on cancer of the breast. He has shown



that groups of cancer cells from the primary tumors in the breast permeate into the lymphatic vessels of the deep fascias of the chest wall. Subcutaneous nodules of recurrences arise only subsequently from the permeated fascial lymphatics along its tributaries. *Fig. 1* shows a number of lymph vessels permeated by cancer cells at points indicated by letters *A, B, C, D, E, F*. At letter *G* there is seen a subcutaneous cancer nodule. This nodule is directly connected with the lymphatics of the deep fascia. As a result of his investigations Handley proposed certain improvements in the radical amputations of the breast for carcinoma. Handley considers the following to be the object in radical surgical removal of cancer. "The removal intact of the permeated area of the lymph vascular system which surrounds the primary growth, and of the lymphatic glands which may have been embolically invaded along the trunk lymphatics of the area concerned." Subsequent investigations have shown that the same rules hold true for the surgical procedures in cancer in every locality.

Modern surgery strives to remove all the normal tissue adjacent to the malignant tumor and into which the latter spreads most frequently and also to remove all regional lymph glands. By the aid of these methods very remarkable results are obtained in the so-called operable cases. However, though between 25% and 50% of this class of cases may remain well for a number of years after the operation, they represent only a small fraction of the whole number of cancer patients seeking relief.

#### *Vital vs. Surgical Statistics*

The writer has reported in a previous publication<sup>3</sup> a comparative analysis between vital statistics and surgical statistics of cancer. This analysis has shown that in the hands of different surgeons the highest percentage of all cancer cases of a community which can be cured by surgical treatment, is 15.25% and the lowest 4.15%, or in all, probably less than 10%. Even on the supposition of the unattainable ideal, that instead of only a small percentage of the cancer patients reaching the surgeon in the operable stage of the disease, all the patients should come to the surgeon early, less than 20% of all the cancer patients may be expected to be cured by the surgical methods employed to-day. Withal the technique of cancer surgery has probably reached its limits.

J. M. T. Finney, of Batlimore, discussing the paper "The Cure of Cancer and Cancer Cures," presented by A. D. Bevan, of Chicago, before the meeting of the American Surgical Association in 1910, stated as follows: ". . . I do believe that we have almost reached our limit so far as this is concerned, that is,

with regard to technique. We cannot make much wider dissections than we are doing . . ." This statement represents the true situation in connection with the surgical treatment of malignant tumors. The latter are usually situated in close proximity to the vital organs, the injury of which would endanger the life of the patient, consequently there is set a limit to the length to which a surgeon may go in removing normal tissues adjacent to the tumors. As a result of these limitations there may remain small islands of cancer cells in or near the operating field, even after a radical operation. For this same reason the knife may inadvertently cut into such an island of tumor tissues and throw freed cancer cells into the opened lymph and blood channels; the malignant tumor will then recur in the same region or in a distant organ.

A further reason for the failure of a radical operation consists in the fact that even in early operable stage of the disease there may be present minute tumor nodules in the distant organs which cannot be detected by any diagnostic means at our command, but which after the operation develop into large metastatic tumors.

It is thus self-evident that the need for the additional methods of treatment of cancer is great. The actual results frequently obtained by surgery alone without the aid of the other methods is very well illustrated in the following report of R. Peterson,<sup>4</sup> of Ann Arbor. He presented a paper on "The Radical Abdominal Operation for Cancer of the Cervix" before the meeting of the New York State Medical Society in 1920, in which he reports that 40.9% of all the operated patients were permanently cured. However, he operated only on 60 out of 380 patients with carcinoma of the cervix which came to him for treatment. Thus in reality 18 patients, or 4.7%, of the whole number were cured, while 14 patients died as the immediate result of the operation. One wonders whether the total result would not have been as good if all the 380 patients remained without any treatment. Nevertheless, Peterson makes the statement in his concluding remarks that if massive doses of radium are required then the patients must be treated with surgery alone because many places in this country do not possess any radium. It would seem to the writer that in a well-organized human society means ought to be found to refer these 380 patients to institutions which possess all the means for treating the disease.

#### *Radiotherapy in Cancer*

The term radiotherapy is usually applied to treatment both by the aid of radium and the X-rays. It is as yet impossible to ascertain whether there is a qualitative difference between the biological and therapeutic action of the two types of radiation. It seems

<sup>3</sup> W. Sampson Handley. *Cancer of the Breast*. London, 1906.

<sup>1</sup> I. Levin. *Medical Record*, April 5, 1919.

<sup>4</sup> R. Peterson. *N. Y. State Journal of Medicine*, 1920, xx, 313.

that the more penetrating the radiations are, the more selective is their biological action, and the Gamma rays of radium are more penetrating than the hardest X-rays at our command. None the less the Gamma rays of radium represent from the standpoint of physics only a more perfect type of X-rays, and the action of the two types of radiations must be to a degree analogous.

The morphologic changes which occur in carcinoma or sarcoma tissue under the influence of radium and X-rays are observed in the tumor cells themselves, and are manifested by the vacuolation of the protoplasm, pyknosis of nuclei, karyoclysis and, ultimately, complete necrosis of the cell. The cellular changes are accompanied by a round-cell infiltration, which is subsequently changed into dense sclerotic connective tissue, poor in blood vessels. This new connective tissue formation ultimately dominates the picture to such an extent that some observers maintain it is the only direct effect of radiation, while the destruction of the tumor cells is secondary and due to lack of nutrition.

#### *The Biological Action on the Cancer Cell*

The clinical, pathological and biological studies of the writer in association with B. Joseph<sup>5</sup> and M. Levine,<sup>6</sup> indicates that the first effect of the rays is exerted directly on the tumor cells. This effect consists in the inhibition of the proliferating power, in the sterilization, as it were, of the cancer cells. The degeneration and destruction of the cancer cells and the formation of the sclerotic connective tissue take place subsequently through the action of the rays; moreover this cell degeneration and cell death may not be due directly to the action of the rays, but takes place in the natural course of the life cycle of the cancer cell. This cycle consists of *youth*, or period of development; *maturity*, or period of function, and *senility*, or period of degeneration, which gradually leads to death. In parenchymatous organs, like the liver and kidneys, the first period is usually completed during embryonic life or at a very early age; the second period continues through the whole life of the organism, and the third period is attained at the old age of the organism or near its death.

The life of an individual cancer cell, on the other hand, is very short; it changes rapidly from an embryonic into an adult and then immediately into an aged, degenerated cell, and this process takes place continually, irrespective of any intrinsic aid. But in a malignant tumor the majority of cancer cells are quickly rejuvenated before they reach senility through the fact that each cancer cell is divided into two young daughter cells. The radiations arrest the

division of the cancer cell, and as a result the latter matures and degenerates. A certain number of such mature cells may not degenerate and though potentially cancer cells, may become resistant to the rays.

The round-cell infiltration, which surrounds the groups of irradiated cancer cells and which is subsequently changed into dense sclerotic connective tissue, is of secondary occurrence, though for practical purposes it is of greater importance than the destruction of the cancer cells themselves. The important rôle of this connective tissue consists in the following: After the most perfect results of radiation, as stated above, there may remain a certain number of viable though stunted cancer cells; the dense connective tissue wall surrounds these cells and keeps them in check. The formation of the connective tissue around the rayed cancer cells is not due to the direct influence of the radiations, and raying of other conditions like thyroid gland, cheloid, etc., is not followed either by cell infiltrations or by connective tissue formation. The experimental investigations of the writer<sup>7</sup> also indicate that this connective tissue formation apparently represents an attempt by the organism to protect itself against the further growth of the cancer by walling it off from the normal tissues by a connective tissue barrier.

It is evident from the study of the mechanism of the biological and therapeutic action of the radiations that it is superior theoretically to surgery because it may either destroy *in situ* or inhibit malignant tumor tissue without injuring or removing any of the adjacent normal tissue. Thus theoretically radiotherapy is the nearest approach to a specific method of treating cancer we can conceive of to-day. However, as will be shown later in practice, radiotherapy notwithstanding its biological advantages has its limitations as well as has surgery.

#### *Radium Therapy*

During the last decade there has accumulated a large number of cancer cases which were treated by radium alone without the aid of surgery or any other method of treatment. As an instance it may be well to cite briefly the report on the radium treatment of uterine cancer, which C. F. Burnam,<sup>8</sup> of Baltimore, presented at the same meeting with R. Peterson before the New York State Medical Society in 1920. Together with H. A. Kelly they treated, up to 1919, seven hundred cases of uterine, cervical and vaginal cancers, and had excluded from treatment only sufferers with advanced general carcinomatosis. Of the cervical cancers irradiation alone cured 50% of the operable cases, 31% of the border line cases, 9% of the inoperable cases and 11% of the recurrent inop-

<sup>5</sup> I. Levin and B. Joseph. The Journal of the American Medical Association, 1917, LXIX, 1068.

<sup>6</sup> Isaac Levin and Michael Levine. Annals of Surgery, April, 1918, p. 443.

<sup>7</sup> I. Levin. Journal of Experimental Medicine, 1911 XIV, 139.

<sup>8</sup> C. F. Burnam. N. Y. State Journal of Medicine, 1920 XX 316.

erable cases. In a previous publication<sup>3</sup> the writer has shown from the results of his own and other investigator's work, that conservatively 6.7% of the inoperable cases may be clinically cured by radium. It will be shown later that good results may be obtained by X-ray therapy alone. However, there are reasons within the physical qualities of these two types of radiations why radium is a more efficient agent than the X-rays.

It has been stated previously in this article that the harder the rays the more selective and consequently the more efficient therapeutically is their action. The Gamma rays of radium are by far the most penetrative rays known to us to-day. The following phenomenon in the physical behavior of the radiations presents another and a most important proof of the greater therapeutic efficiency of Gamma ray of radium over that of X-rays. A beam of rays, when it leaves the point of its formation, travels in the form of a pyramid. The further away from the apex this beam travels the more diffused it becomes. The closer therefore a square unit of the surface of a body is to the apex of the pyramid the greater the intensity of the rays.

It has been shown that the diminution of this intensity is in inverse ratio to the square of the distance of the surface of the body from the source of the rays. The Gamma rays of radium are formed from every molecule of a radium salt or from every atom of radium emanation; consequently when a small cylindrical tube of radium is placed over the surface of, or better still within, a tumor, the distance between the source of radiation and the tissue to be affected can be made almost infinitesimal. The X-rays, on the other hand, originate at the focal point of the target of an X-ray tube which is in itself 10-15 c.m. from the bulb surface. In reality in X-ray therapy the distance due to the physical and mechanical conditions of the apparatus between the focal point and the surface to be affected is between 30 and 50 c.m. To this must be added 10 c.m. or more, being the distance from the skin to the tumor. As a result a far greater quantity of the X-rays must enter the organism of the patient in order to obtain at the tumor the quantity needed to influence it. The radiations are, however, not indifferent to the rest of the organism, but produce a reaction on normal tissues and particularly on the blood and blood-forming organs, which may become so severe as to counteract the beneficial effect of the rays on the tumor, since the irradiation, as was stated above, must be accompanied by a great deal of protective co-operation on the part of the blood and lymphoid tissue.

#### *The Action on Blood and Lymphatic Tissues*

The writer conducted, in association with M. M.

Sturges,<sup>9</sup> an experimental investigation, which shows this difference in the action of the two types of radiations. The study consisted in an analysis of the blood of frogs and rabbits after treatment with X-rays or radium. The whole body of the animals were treated with the same quantity and quality of X-rays. The radium treatment consisted in the introduction by a method to be described later into the dorsal lymph sack of a frog of a minute capillary glass tube about 4 mm. long containing from 1.0 to 0.6 millicuries of radium emanation. In the rabbit a laparotomy was performed and from two to four radium emanation capillaries were inserted into the spleen.

The difference observed in this investigation in the reaction of the blood to the X-rays and radium on frogs and rabbits is quite significant.

A similar amount of X-raying produced a similar change in the blood of a rabbit as it did in the frog. On the other hand, an insertion of radium in the frog produced a similar change in the blood of the animal as the X-rays, an insertion into the spleen or the bone marrow of a rabbit of 2 to 4 capillaries, i. e., of 2 to 4 times the amount of radium emanation used on a frog, produced no change in the blood of the rabbit whatever, though it produced a deep local effect on the spleen and bone marrow tissue.

Biologically the amount of X-rays used on the frog must equal the amount of radium emanation contained in the capillary since the biological results obtained were identical. A larger amount of radium emanation used on the rabbits must have produced some general biological effect on the blood of the animal since it produced such an effect on the blood of a frog. However, the effect on the blood of the rabbit was apparently so small when distributed over the comparatively large amount of blood and blood-forming tissue of the rabbit that it produced no tangible result on it and did not change its structure.

The comparison in the action of the X-rays on the two species of animals, on the other hand, shows that the same technique produced the same general effect on the blood of a rabbit as on the blood of a frog. The reason for it lies in the fact that the quantity of the X-rays entering the animals must be multiplied by the square of the surface of their bodies, consequently the rabbit obtained a greater quantity of radiation.

These experimental results tally well, as will be shown later, with the clinical findings. The advantage of radium over the X-rays, generally speaking, consists in the fact that the same local effect can be obtained by the former without the general reaction which is frequently so severe in modern X-ray therapy.

<sup>9</sup> I. Levin and M. M. Sturges. *Proceedings of the Society for Experimental Biology and Medicine*, 1921, XVIII, p. 295.

### The Technique of Radium Therapy

The method of using radium for therapy which was generally employed heretofore consisted either in sealing an insoluble salt of radium element in a glass tube or in a small hollow needle built of irido-platinum or "non-corrosive steel" or else in incorporating the radium salt in a varnish and spreading it over the surface of a flat applicator.

This method lacks, however, both flexibility and compactness and is very unwieldy for utilization of large quantities of radium. While occasionally a whole gramm may be used on one patient, it is frequently necessary to use as little as 0.3 of one milligram for one area of a tumor.

The more recent method of employing the so-called "radium emanation" obviates many of these difficulties. It is very compact (an equivalent of 1 gm. of radium element may be condensed into 0.6 of a cubic millimeter) and flexible, since the available quantity may be divided in any desired manner. As

emanation, the writer will permit himself to digress into a brief discussion of the physical qualities of the salts and the emanation of radium.

### The Physical Characteristics of Radium

Radium is an elementary body with an atomic weight of 226.4. Its so-called radioactivity is due to the fact that it constantly emits alpha, beta and gamma rays, of which the two latter are employed in therapy. These rays are emitted in the course of the disintegration of the atom of radium. The radium element emits only an alpha ray and is thus transformed into "radium emanation," or "niton," which is also an elementary body, but has the structure of a heavy gas, the atomic weight of which is 222.4, *i. e.*, 4. (the atomic weight of helium or the Alpha particle) less than the atomic weight of radium. Radium emanation also emits only alpha particles and is then disintegrated into a series of new elementary bodies so called Radium A, Radium B and Radium C, which are solid bodies. Only the latter two substances (Radium B and Radium C) emit beta and gamma rays and have a therapeutic value. Consequently, for purposes of therapy the results will be identical, whether radium salts or radium emanation is the source of radioactivity. They will both have to disintegrate into Radium C before they can be employed.

Since it takes the radium element about 1700 years to lose a half of its amount through disintegration, it is obvious what a small fraction of it changes into radium emanation during each unit of time. The first advantage of the latter substance over the radium salt is thus evident; it may be concentrated into smaller space. The radium emanation, though heavy, can be collected and manipulated like any other gas. To obtain it from the radium the latter has to be kept in solution in a flask which is directly connected with a system of mercury pumps.

Fig. 2 shows a photograph of the apparatus used in the writer's laboratory. The radium salt is dissolved in water acidulated with hydrochloric acid in glass flasks, which are placed in a lead-lined safe. The flasks are joined to one glass tube which leads out from the safe into the collecting apparatus. The latter, as stated above, consists of a system of mercury pumps connected with a highly efficient electric pump. The object of the apparatus is the following: a vacuum is created in the flasks containing the radium solution. As a result the radium emanation gas, together with hydrogen, oxygen and chlorine formed in the flasks under the influence of the radiations, as well as water vapor and other gases forming as impurities in the apparatus, collect in the glass tubes and flasks of the latter. Of all these gases the radium emanation occupies the smallest space. The apparatus, which was designed originally by Prof. Duane,<sup>10</sup> of Harvard

<sup>10</sup> Wm. Duane. Boston Medical and Surgical Journal. 1917. CLXXVII. 787.

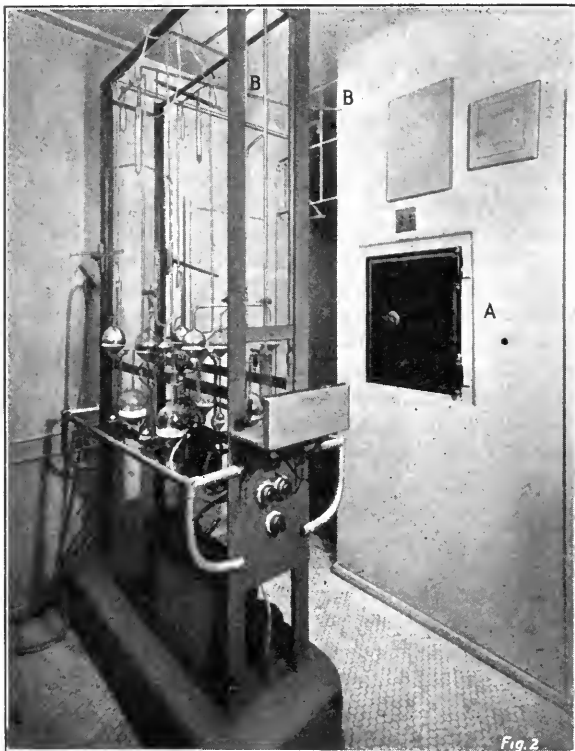


Fig. 2. Photograph of radium emanation apparatus in the writer's laboratories. A—Safe containing the radium solution flasks; B—The glass tube leading from the flask to the set of pumps.

will be seen later, the use of radium emanations is creating entirely new and very promising methods of radium therapy. Before discussing further the developments in therapy produced by the use of

University, contains, besides the vacuum pumps, a purifying apparatus to absorb the additional gases and thus obtain the pure concentrated radium emanation gas. Fig. 3 presents schematically the apparatus employed in the writer's laboratories. It consists of two independent units, so that when one unit becomes defective the other may be used while the former is

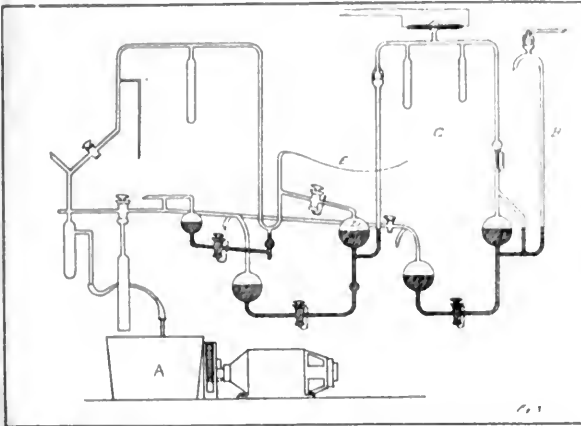


Fig. 3. Schematic drawing of the set of pumps of the emanation apparatus. A—Electric pump; B—Tube leading from safe; C—Purifying system; D—Last receptacle flask; E—Capillary glass tube.

being corrected.

When the purification of the emanation is complete it is driven into the last receptacle flask (Fig. 3d) of the apparatus and from there into a long capillary glass tube (Fig. 3e). The capillary is then sealed off and divided into small tubes of from 12 to 3 mm. long and about 0.5 to 0.3 mm. in diameter. The longer capillary tubes are immediately placed in silver capsules  $\frac{1}{4}$  mm. thick and 16 mm. long, coated with multi-colored enamel for the purpose of identification. Three and one-half hours later, when a sufficient amount of radium emanation has changed into radium A, B and C, and the gamma ray activity within the capillaries reached its equilibrium, the contents of the tubes are measured by the aid of an electroscopes or galvanometer type of measuring apparatus. The principle of the measurement is based on the fact that the gamma rays of radium ionize the air within the ionization chamber of the apparatus and the intensity of this ionization is commensurate with the quantity of the gamma rays of radium. This indirect method is the only one at our

command to measure either the quantity of radium salts or radium emanation. The unit of measure for radium emanation is one millicurie, which means the amount of gamma rays equal to an amount emitted by one milligram of radium element.

Fig. 4 shows another division of the radium laboratories of the writer containing the electroscopes and galvanometer. Unlike the tubes containing the salts the amount of radium emanation within the capillary is constantly changing and therefore a complete record of each tube has to be kept.

#### Surface Application of Radium Emanation

To prepare the emanation tubes for use on patients, several tubes of a desired strength are placed parallel in wooden or brass boxes of the necessary dimensions. These boxes act as additional filters since the glass and the  $\frac{1}{2}$  mm. of silver of the tubes filter off only the alpha and softest beta rays and create the correct distance between the radium and the surface of the tumor to be treated. When the configuration of the diseased area is irregular a perfect mould can be prepared of dental compound and the tubes spread on it. Fig. 5 shows applicators for various parts of the body.

By all these methods a more or less large quantity of radium emanation is placed at one of the surfaces of the tumor, left for a number of hours and then removed. Even when an applicator is placed inside of an organ, like the rectum, uterus, esophagus, etc., in relation to the tumor itself, the radium is placed on the surface of it.



Fig. 4. The measuring division of the writer's radium laboratories. A—Electroscope; B—Reflecting screen; C—Protection for operator; D—Galvanometer; E—Experimental ionization chamber used in research work.

### Intratumoral Application of Buried Tubes of Radium Emanation

This method presents a comparatively new departure in radium therapy, but the results up to the present are so gratifying that the writer is convinced that it is certain to play a most prominent part in the future development of the whole field of radiotherapeutics. For this method the radium emanation and not the

long, containing between 0.3 and 1.5 millicuries of radium emanation are inserted by the aid of a trocar (Fig. 6) into the tumor tissue and left there. The capillaries may be sterilized either by boiling or immersion in a solution of iodine and then in alcohol. These tubes exert a comparatively weak but continu-

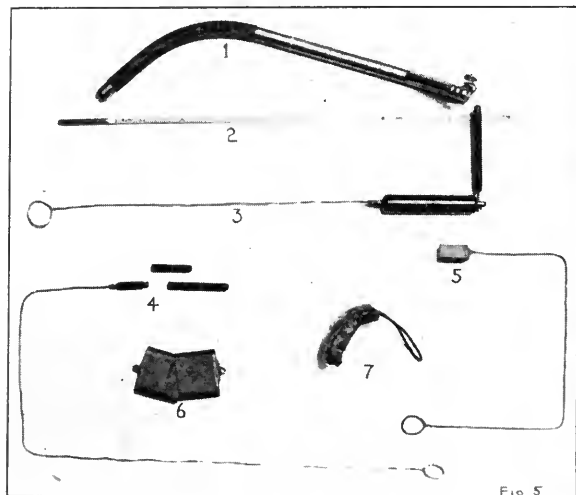


Fig. 5. Set of applicators for surface application of radium. 1 and 2 shows an intralaryngeal applicator devised by Dr. S. Yankauer. 3 is a rectal applicator devised by the writer, the perpendicular rod of hard rubber is used for protection of the operator while opening and closing the applicator. 4 shows an applicator which may be used for oesophagus or as an intracervical applicator. 5 shows a brass box in the form of a pyramid. 6 in the form of a match box. 7 shows a special mould of dental compound to conform to a case of carcinoma of the tongue.

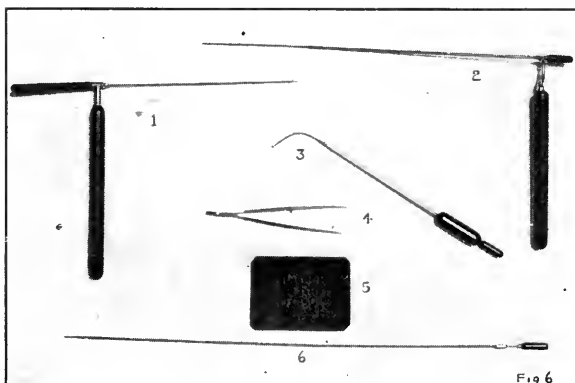
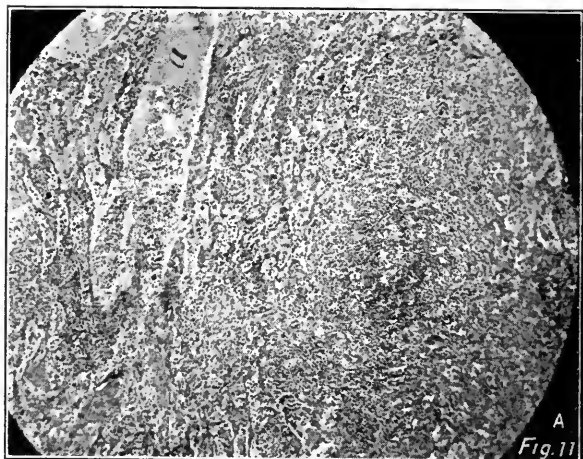
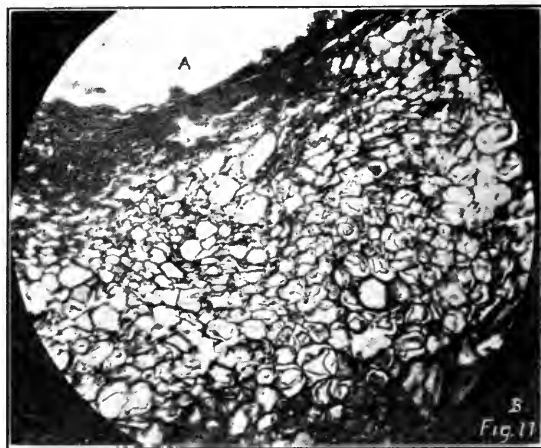


Fig. 6. Set of trocars for insertion of bare tubes of radium emanation. 1 and 2 show different length of straight trocars. The hard rubber handles are for protection of the hands of the operator. 3 a curved trocar. 4 a flexible trocar used with Dr. L. Buerger operating cystoscop. 5 a thumb forceps. 6 a number of bare capillary glass tubes filled with radium emanation.

salts of radium must be employed. The technique is as follows: Bare capillary tubes about 3-5 mm.



A  
Fig. 11



B  
Fig. 11

Fig. 11. A shows a microphotograph of a portion of a spleen of a rabbit into which a bare tube of radium emanation was inserted. At A is seen the necrotic area; B microphotograph of a crown gall into which a bare radium emanation tube was inserted; A shows a protecting cushion of cellulose surrounding the necrotic area.

ous action on the tissues which lasts for several weeks. The cumulative action of one millicurie is calculated to equal 132 millicurie hours, or in other words, equal to one milligram of radium salt applied to the same area for 132 hours. However, the action exerted on tissues by the buried tube of emanation is entirely different qualitatively from the surface application.

Depending upon the mass of the tumor, several



such tubes are inserted at accurately determined distance from each other and also at a correctly safe distance from the neighboring normal tissues. The tumor tissue immediately surrounding the capillary is influenced by the soft beta rays and becomes necrotic. (Fig. 11.) This area of necrotic tissue seems to act as a filter and the next zone of tumor tissue is influenced only by the hard beta and gamma rays. As an ultimate result the tumor is replaced by a connective tissue capsule which wholly encloses the glass capillary, which by that time becomes inert and causes no discomfort to the patient. The studies of the writer with Dr. M. Levine on crowngall—a plant tumor—have shown that the necrotic area is surrounded by a protecting cushion of cellulose.

#### *Advantages of the Method*

Tumor tissue is destroyed much more promptly and by a much smaller quantity of radium by this method than by surface applications. The necrotic area surrounding each capillary is very small, and if they do not contain much more than one millicurie of emanation and the tubes are not placed too close to each other, there does not take place any severe general sloughing. In the course of the last two and a half years the writer has used this method extensively in cases of intraperitoneal tumors (carcinoma of the gastrointestinal tract, the uterus and ovaries, hypernephromata and retroperitoneal tumors). A laparotomy is performed and when it is found that the tumor itself is inoperable, *i. e.*, cannot be radically removed, then instead of palliative procedures or mere exploration, emanation tubes are introduced into the tumor. The patients make an uneventful recovery, there is no rise of temperature, no peritoneal irritation or subsequent sloughing of the tissue. In a word, the insertion of radium emanation does not add in the least to the hazard of the operation. The tumors shrink considerably and the final effect of the irradiation is usually noted in about six weeks.

This method seems to present an ideal combination of surgical removal and an irradiation. Each such intratumoral insertion of radium emanation should be followed by surface applications of radium emanations or by X-ray treatment of the periphery of the tumor for purposes of prophylaxis.

#### *The Efficiency of Radium*

The perusal of the foregoing pages and a close analysis of the mechanism of the action of the various methods of radium application clearly indicate that radium is the most efficient single agent in cancer therapy. Intratumoral application of radium may destroy the primary malignant tumor as completely as does surgery. A surface application of a few grams of heavily filtered radium at a distance of, say, 30 c.m. from the skin of the patient, will on the other

hand, deliver a beam of rays by far more homogeneous and penetrating than any machine constructed by human mind and hands ever will be able to do. The efficiency of radium is in reality limited less by its potentiality than by its cost. It is the writer's conception that radium should stand in the center of the problem of cancer therapy, and surgery and X-ray therapy be placed at both ends as complementing the action of radium. If the statement is still generally made that surgery is the main method of therapy and all radiotherapy is only assisting the latter, this is merely a concession to the former achievements of surgery. In the next chapter an attempt will be made to give a true evaluation of the place of the X-rays in cancer therapy.

#### *X-Ray Therapy of Cancer*

The development of the methods of X-ray therapy may be roughly divided into three periods. In the first period, which continued from the beginning to about ten years ago, no attention was paid to the quality of the radiations nor to the ratio between the quantity of radiations which were directed upon the surface of the body of the patient and the fraction of these which reached into the depth. In the second period, which began about ten years ago, through the improvement in the X-ray machine (higher voltage on the secondary) and in the quality of X-ray tubes, particularly the development of the Coolidge type of tube, and the use of filters, X-rays of smaller wave length and consequently higher penetration were obtained. Furthermore, by the use of several small fields of entry and by cross-firing from opposite directions an empirical attempt was made to obtain in the depth a greater fraction of the quantity entering through the skin without injuring the latter. Nevertheless this fraction still remained very small and its quantitative relation to the total entering the skin could not be determined.

The latest developments in the X-ray therapy, which have taken place in the course of the last five years, consist, first, in the construction of X-ray machines which produce 200,000 volts and more in the secondary, and of X-ray tubes which can withstand the high voltage input. Furthermore, the ionization methods of measuring the intensity of X-rays were perfected so that it is now possible to determine with a fair amount of accuracy the percentage of the surface amount which penetrates into a certain depth. These measurements brought forth the following striking result which even *a priori* supports the writer's contention stated above as to the difference of the action of radium and the X-rays. The percentage of the quantity of radiation entering the depth of about 10 c.m. even with the most powerful machinery and tubes and with  $\frac{1}{2}$  mm. of zinc or 1 mm. of copper as filter, is comparatively small. In

order to improve this quotient of the depth dosage to the intensity of the rays on the surface, not several small fields, but a large portal of skin entry must be used. The reason for it lies in the fact that the quotient of the depth dosage can only be improved by the addition of secondary and scattered radiations which are formed within the tissues by the entering beam of rays. The larger the portal of entry, the greater the quantity of secondary and scattered radiations, and in order to obtain the necessary quantity in the depth a large field must be used.

Kronig and Friedrich,<sup>11</sup> who added more than any other group of investigators to the progress of the subject, have shown experimentally that while in accordance with theoretical calculations only 10% of the surface intensity of the X-rays reaches into the depth of 10 c. m., even with a voltage of 20,000 and 1 mm. of copper filtrations, the actual percentage as measured by the ionization method is as much as 43%. They further show the following relationship between the size of the field of entry and the quotient of the dose in the depth. Given the same conditions, namely, 20,000 volts, 50 c.m. target skin distance, 1 mm. copper as filter, a field 5 c.m. square delivers 31% of surface intensity into 10 c.m. depth, a field 10 c.m. square delivers 38% and a field 15 c.m. square 43%. They have further shown the existence of secondary radiations at a considerable distance to the periphery of the field of entry. All this means that in order to direct the necessary quantity of radiations to a deep seated tumor a large quantity of radiation will also be directed to the adjoining normal tissues, the blood and the blood-forming organs. Furthermore, if an attempt is made to send a very large dose in the depth from several portals of entry, a cumulative effect may take place at some point in the depth, with consequent serious injury of normal tissues.

#### *The Newer X-Ray Apparatus*

There is no doubt that technically the high-voltage X-ray machines and the ionization method of measuring the intensity of radiation mark a great progress

in X-ray therapy and are indispensable in the treatment of cancer. The writer still uses the old type machines for the treatment of Hodgkin's disease, leukaemias, splenomegalies, exophthalmic goiter, surgical tuberculosis, etc. For the treatment of cancer, however, the writer employs now only the high-voltage machines. Fig. 7 shows the installation in the writer's private laboratories. The units of apparatus were built by Waite & Bartlett Company, and Dr. Waite co-operated with the writer and used much ingenuity to create a set of machines which will lose



Fig. 7. The high voltage X-ray apparatus in the writer's laboratories. A shows the adjustable table; B the generation machine; C the Coolidge filament transformer; D the sphere gap; E the box containing the X-ray tube; F the milliammeter; G the pyramid; H iontoquantimeter; I insulated tube from the electroscopes to the ionization chamber under the pyramid; J exhaust fan to purify the air of the room.

nothing in their efficiency and at the same time be so compact as to fit in any X-ray laboratory. The generating machine presents a double transformer with a double cross arm mechanical rectifier operated by one synchronous motor. The X-ray tube is completely incased in a rigid ray-proof box, the whole room is leaded throughout, and photographic tests have shown that no rays penetrate beyond the room and box, thus protecting the operating staff and the people in the vicinity from the action of the rays. A sphere gap measures and controls the voltage entering the tube. A controlling device connected with the rheostat of the filament transformer keeps the milliamperage perfectly constant. The table can be raised and lowered.

<sup>11</sup> B. Krönig und W. Friedrich. *Physikalische und biologische Grundlagen der Strahlentherapie*. Berlin, 1918.



The writer had constructed a set of frames in the form of pyramids which have at one end a lead diaphragm under which is attached the filter  $\frac{1}{2}$  mm. or 1 mm. of copper and 1 mm. of aluminum. At the other end of the frame there is attached a plate of bakelite which filters off the secondary radiations produced by the metal filters. The respective square dimensions of the opening in the lead diaphragm and

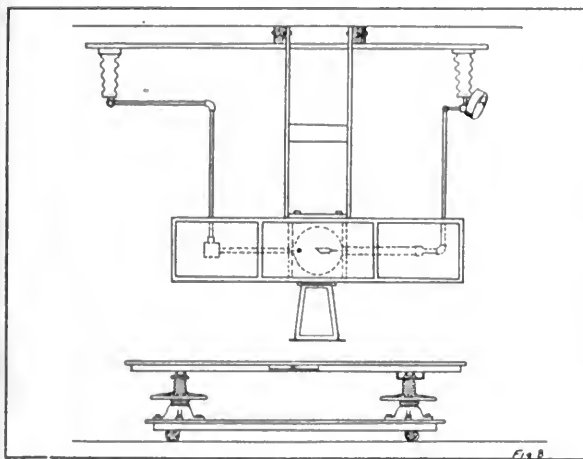


Fig. 8. A schematic cross section drawing of the X-ray tube, tube box, millimeter, pyramid and treatment table, showing the relative position of the parts.

the piece of bakelite at the base of the pyramids are so arranged that the beam of X-rays passing through the diaphragm has the square size of bakelite, when it reaches it. Furthermore, the height of the pyramids is such that when the bakelite touches the skin of the patient, the distance between the skin and the target of the X-ray tube is exactly 30 or 50 cm. This device simplifies the arranging of the fields of treatment. The proper sized pyramid is selected, placed in the box under the tube and the table raised until the skin of the patient touches the bakelite place of the frame. If the skin does not touch the plate everywhere, then cotton padding is added, which absorbs the rays in the same way as the tissues of the body. Fig. 8 shows a schematic cross section drawing of the arrangement. The writer uses comparatively large fields, 10, 15 or 20 cm. square. The number and size of fields is arranged in accordance with the condition to be treated, the size and location of the tumor and the size of the patient. Fig. 7 also shows the relative position of the ionization measuring apparatus to the X-ray tube. Fig. 9 shows a photograph and schematic cross section drawing of the same apparatus.

The apparatus used by the writer is one devised by Dr. Solomon, of Paris. It is practically identical with Friedrich's iontoquantimeter and consists of an

ionization chamber, which is a small cylindrical tube built of horn and lined with graphite. This ionization chamber is placed directly under the X-ray tube, as shown in Fig. 7. The ionization chamber is con-

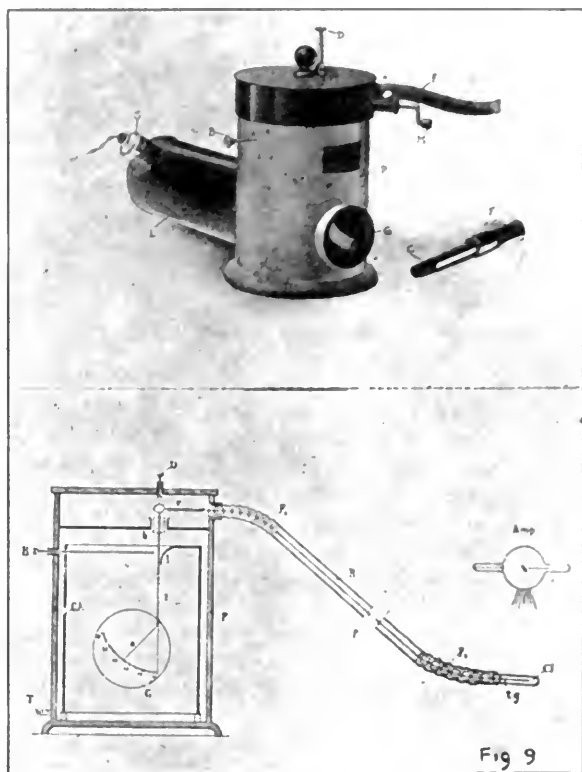


Fig. 9. Photograph and cross section drawing of Dr. Solomon's ionization measuring apparatus. CL—Ionization Chamber; F's R., The connecting tube; P—The lead lined electroscopical; T—The metal rod; A—Silver leaf; G—The scale; M—The charging device.

needed by the aid of graphite lined tubing with an electroscopical. The electroscopical itself is again a large ionization chamber within which there is placed a metal rod, and affixed to it somewhere nearly midway is a silver leaf. A small friction apparatus charges the electroscopical chamber with high-potential electricity (about 300 volts). This electrical charge deflects the silver leaf from the rod. When X-rays or gamma rays of radium enter the ionization chamber the air within that chamber, as well as within the connective tubing and the electroscopical chamber, becomes ionized. As a result of this the high-potential current within the electroscopical chamber is discharged and the silver leaf falls back to the rod. The rapidity with which that fall takes place is in direct ratio to the intensity of the radiations. There is arranged within the electroscopical chamber of the apparatus a scale of numbers running between 10 and 60 and a

reflecting glass. The measuring with this apparatus proceeds in the following way: The electroscope is charged until the leaf is deflected to 60; then gamma rays of radium or X-rays are directed to the small ionization chamber for as long as it takes the leaf to drop to 10 on the scale. The time necessary for it is measured by a stop watch. The apparatus is so standardized that the gamma rays from 1 gm. of radium take one second to move the leaf from 60 to 10. The unknown intensity of the radiations acting on the ionization chamber can consequently be measured when the time it takes the leaf to move from 60 to 10 is known. This ionization apparatus is very similar to the one described above which is used for measuring radium emanation.

### Measuring Dosage

When an X-ray machine and X-ray tube are so constructed that the voltage on the secondary, or rather to say, the voltage entering the tube and the miliamperage do not fluctuate then given the same distance from the target to skin and the same filter the intensity of radiations delivered in a unit of time will practically be always constant, and it is therefore not necessary to measure it frequently with the ionization method, but it suffices to use the latter only at intervals for proper control.

Thus, with the new methods and the modern apparatus, an exactly calculated amount of radiations may be delivered into the depth. Through a large field of entry 43% of the skin dose may be delivered to a deeply seated tumor and with several portals of entry even more than a skin dose may reach the tumor. However, too much emphasis cannot be laid on the fact that such a large amount must be accompanied by dangerously intensive raying of adjacent normal tissues. Attempts were made in the gynecological clinics of Freiburg and Erlangen not only to measure the quantity penetrating into a certain depth, but also the exact quantity needed to destroy a malignant tumor. A so-called carcinoma dose is claimed to represent 110% of a skin dose, while a sarcoma dose represents 70% of a skin dose. Such conceptions represent only a very rough estimate of the true situation. The biological behavior of a cell cannot be translated into an arithmetical equation. A melanosarcoma is, for instance, by far more resistant to irradiation than carcinoma, while a lymphosarcoma can be influenced by a very small fraction of the quantity needed for any other type of malignant tumors. Furthermore, no account is taken of the fact that the efficiency of radiotherapy in cancer is in inverse ratio to the mass of the tumor. The greater the amount of the total tumor mass within the organism, the more malignant

is the condition clinically and the lower is the power of resistance of the organism. The writer has shown in a previous publication<sup>12</sup> that even metastases in the bones may be clinically arrested when they are not multiple and the primary tumor is removed, while the existence of several metastatic tumors in the skeleton make the condition hopeless. Moreover, the measure of the true quotient of the depth dose can never be made mathematically accurate.

Holfelder<sup>13</sup> claims to have devised an accurate method. He employs, in accordance with the technique of Seitz and Wintz, several not very large fields of entry. A set of colored celluloid plates overlapping each other and laid over a flat schematic

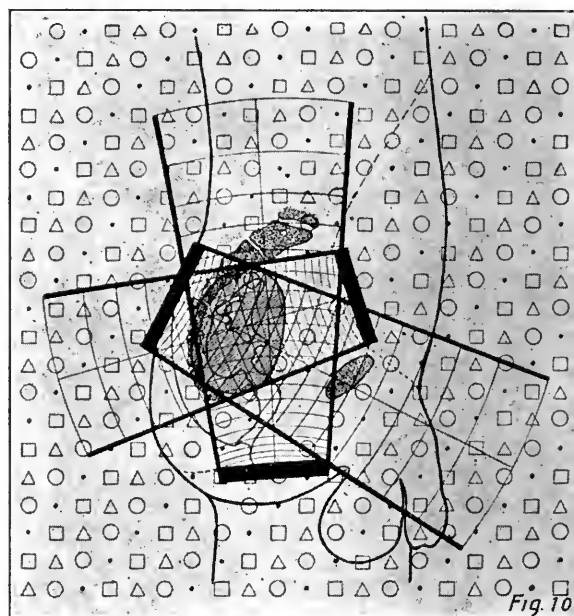


Fig. 10. From Holfelder<sup>13</sup> a scheme of his field selector for carcinoma of the rectum. Three celluloid plates overlapping at the site of the tumor.

drawing of the patient filled with dots, circles and triangles, into which the tumor is drawn, arranges the combination so that within the area of the tumor all the figures on the paper are obliterated by the depth of the color of the overlapping plates, and this represents the required full carcinoma dose. This device he calls a field selector. He then directs the X-ray tube under the same angles to the surface of the body as the celluloid plates. Fig. 10 shows, however, that the field over the abdomen is applied with pressure which of necessity must change constantly during the treatment. Furthermore, the slightest

<sup>12</sup> I. Levin. *Annals of Surgery*, 1917, 327.

<sup>13</sup> Holfelder. *Strahlentherapie*, 1921, XII, 161.

movement of the patient changes constantly the relative positions of all the fields and consequently creates the danger of an overdose and severe injury to the normal tissues.

#### *What of X-Ray Therapy Alone?*

Seitz and Wintz, of Erlangen, maintain that it is possible to cure carcinomata of the cervix with X-rays without the aid of any other agent. They support their view by the fact that of twenty-four cases so treated twenty-three remained well for one year. This is a premature and ill-advised assertion. Such an attitude does more harm than good, both to X-ray therapy and, as well, to cancer therapy as a whole.

It may be appropriate to cite a couple of facts from the work of Freiburg and Erlangen to indicate that X-ray therapy alone cannot be considered the correct treatment of every cancer case. Friedrich and Behme<sup>14</sup> reported from Freiburg on a series of seventeen cases of cervical carcinoma treated with X-rays alone. Five cases were given a so-called full carcinoma dose through the abdomen and back. All the five patients suffered from X-ray cachexia and severe blood changes as a result of the treatment, and the cervical carcinoma was not influenced by the treatment. The other twelve cases were treated through the vagina with better local results and less general effect on the blood, which was due to the small field of entry. The authors conclude that the general ill effect on the organism when large fields of entry are used, influence unfavorably the local effect of the rays on the tumor. Now, it stands to reason, that X-ray treatment applied through the vagina must be less efficient than radium applied directly into the cervix or the endometrium. The authors attempted to bring the rays nearer to the cervix by making a deep perineal incision, but this resulted in local implantation of carcinoma.

#### *The X-Ray Plus Surgery*

Seitz and Wintz<sup>1</sup>, who as stated above, claim to have received good immediate results with treatment of cervical carcinoma, presented in the same publication a very instructive report on the treatment of forty-two cases of ovarian carcinoma. Nine cases were treated with surgery alone, ten cases with X-rays alone and both without any results. Twenty-three cases were operated, the main tumor masses were removed and then X-ray treatment was instituted, and the result in these cases was a great deal more favorable. They conclude that ovarian carcinoma cannot be irradiated without a previous operation since the full dose produces a "Roentgen-cachexie." Apparently a full carcinoma dose in cervical carcinoma and ovarian carcinoma are differ-

ent things. In this instance the difficulty is caused by the mass of tumor, since ovarian carcinoma is more radio-sensitive than cervical carcinoma.

Yungling,<sup>15</sup> of the surgical clinic of Tubingen, working with the exact Erlangen methods, found that X-ray therapy alone, using a full carcinoma dose, gave poor results in carcinoma of larynx, lip, tongue or rectum.

The progress of X-ray therapy in the course of the last decade is due to a large extent to the fact that the German gynecologists became interested in the subject. The weakness of their stand, however, lies in their premature generalizations. Results obtained on carcinoma of the cervix and uterus cannot be transferred to cancer in other localities. The uterus and cervix is a muscular organ, which is less radio-sensitive than carcinoma and presents a good protection against insults of all kind. Carcinoma of the rectum or esophagus, for instance, is very poorly protected by the thin walls of these organs. Carcinoma of the larynx is situated immediately over cartilage which is fully as radiosensitive as carcinoma tissues, and so on. Though the newest methods of X-ray therapy represent a great progress and must supersede all the previous methods of X-ray therapy, this agent cannot be considered an all-sufficient method of cancer therapy and is undoubtedly not as efficient as surgery alone or radium therapy alone.

#### *Combined Methods of Cancer Therapy*

There is no doubt that basic limitations to all the three methods of cancer therapy exist, which will be impossible to overcome by further progress in the technique. The limitations of surgery were analysed above. Both radium and the X-rays exert a truly specific selective action on cancer tissue, and biologically they present the nearest approach to a specific therapeutic measure. The limitations of both agents are due mainly to the size and location of the tumors and the comparative vulnerability of the normal tissues. Radium can be placed in near approximation to or within the tumor. The new method of buried radium emanation capillaries obviates to a great extent the difficulties created both by the size and location of the tumor. However, the size and multiplicity of the malignant tumors make the quantities of radium required prohibitive. Excessive quantities may become injurious to the rest of the organism. X-rays are less costly and may effectively cover simultaneously many areas even in the depth of the organism and influence the tumor nodules, provided they are sufficiently small. Treatment of large tumor masses is followed by severe general reaction of the organism, and, as was seen above, even a so-called full carcinoma dose does not destroy a large tumor. Further progress in cancer therapy must be looked

<sup>14</sup> Friedrich und Behme. *Strahlentherapie*, 1920, XI, 35.

<sup>15</sup> Yungling. *Muench. Med. Woch.*, 1920, no. 24, p. 690.

for in the development of proper methods of co-ordination of the three therapeutic measures.

### Correct Methods Illustrated

It may be well to illustrate in a few instances the correct methods of combined therapy which may be pursued.

The writer had under his care two cases of *carcinoma of the urethra* in the female. In one case a complete radical operation was done with block dissection of regional lymph glands and removal of the whole urethra with sphincter. No other treatment was instituted until three months later, when a severe recurrence took place which did not react to intensive irradiation and the patient died six months after the operation. In another case the writer was consulted before any treatment began. At his suggestion preoperative radium treatment was given and then an incomplete operation was done, removing only the tumor and leaving the posterior part of the urethra and sphincter intact, and this was followed by surface application of radium. The patient is well clinically and is so now, over two years after the operation.

In co-operation with Dr. Seeligman, at his service at the Lenox Hill Hospital, a number of cases of carcinoma of the cervix, vagina, urethra and ovaries were treated by the writer.

As was shown above, the idea of a certain number of German clinicians that every case of carcinoma or sarcoma of the pelvic organs in the female may be cured by a so-called full carcinoma or sarcoma X-ray dose administered through the abdomen and back is not borne out by the results obtained. Best results are obtained by applying a different plan of treatment for each individual case.

Whenever the tumor could not be removed surgically the main reliance was placed on the intratumoral application of buried capillary tubes of radium emanation, which is aided by surface application of radium into the vicinity of the tumor and by X-ray therapy of the adjoining areas.

*Carcinoma of the larynx* is very difficult to handle and the radical operation leaves a very marked deformity. In the great majority of cases the condition recurs promptly and X-ray therapy does not influence the condition. The writer, in association with S. Yankauer, treats these cases in the following manner: Preoperative radium treatment is given externally and intralaryngeally through an instrument devised by Yankauer. Then a suspension operation is done, only the tumor without any adjacent normal tissues is removed, and post-operative radium therapy instituted. One of Yankauer's patients is now well for over five years. Another is well a year and remains with such a good speaking voice that he pursues his occupation as a traveling salesman.

In border-line cases of *carcinoma of the breast* the writer buries radium emanation needles into the breast tumor and the axillary glands, places radium boxes over the tumor and glands, three to six weeks later a radical breast amputation is done, and this is followed by radium treatment of the operative field and supraclavicular region and X-ray treatment of the chest and the parts of the skeleton into which metastases may take place. Dr. Auchincloss, at his service at the Presbyterian Hospital, co-operated with the writer on some of his cases.

*Carcinoma of the urinary bladder* is treated by the writer in co-operation with Dr. Leo Buerger in the following manner: A cystotomy is done and if the tumor is found to be operable then it is removed and a surface applicator is placed in the bladder. If the tumor cannot be removed, then a sufficient amount of radium emanation capillaries is placed into the tumor and the bladder is allowed to close. This is followed by surface application of radium over the symphysis and per rectum and by X-ray therapy. The results of this method are very gratifying and an extensive report will be published shortly by the two investigators.

In co-operation with Dr. J. Lynch, at his service in St. Bartholomew's Hospital, and with Dr. L. Buerger, the writer has treated *carcinoma of the gastrointestinal tract* in the following way: A laparotomy is done, which is followed either by a radical operation or by an exoperation with or without some palliative surgery. In all cases where the tumor is not removed surgically, radium emanation capillaries are placed into the tumor. All the operations are followed by surface application of radium and by X-ray therapy. A preliminary report on this work is in press.

### Conclusions

Cancer therapy requires a great deal of sound judgment and experience in handling complex clinical conditions. A radiotherapist should not undertake to treat a cancer patient without the co-operation of surgeons within the different specialties, nor should a surgeon operate on a cancer case without having an experienced radiotherapist near to hand. No man, be he a clinician or physicist, can create a scheme which will fit all the cancer patients, or, for that matter, any two consecutive cases.

The necessity for early diagnosis of cancer is an axiom in medicine. But even in perfectly apparent advanced cases a correct estimation must be made before a hasty attempt at therapy is made. The writer had under observation a case at his service at the Montefiore Hospital on which two laparotomies were done, by a noted New York surgeon, on a diagnosis of carcinoma of the intestines. When the patient

entered the Montefiore Hospital, two months later, the writer made a clinical diagnosis of an ovarian carcinoma which was subsequently confirmed by an autopsy. If a correct diagnosis were made before the operation and consequently the laparotomy incision made below instead of above the umbilicus, a radical removal of the tumor may have been possible.

Even in attempts at palliative treatment, the correct aim must be kept in mind and a course pursued which will accomplish it. The following case may well illustrate the point: Dr. Leo B. Meyer kindly conferred with the writer in regard to this patient. Mrs. G., a woman eighty-five years of age, the mother of a physician, was suffering from a scirrhus carcinoma of the left breast for several years. For the last two months the tumor began to grow rapidly and cause pain and discomfort. Since the age and general condition of the patient precluded a radical operation, Dr. Meyer thought that palliative radium treatment would be the course to pursue. The examination showed a tumor the size of an orange occupying the middle of the left breast. The tumor was soft and showed apparent fluctuations, the skin over the tumor was thinned, of a bluish red color and firmly adherent to the tumor. One large lymph node could be felt in the left axilla. The writer stated that the tumor would ulcerate very soon and even more promptly if radium treatment were attempted. This would be followed by foul discharge and great discomfort to the patient and surroundings. He suggested, therefore, that an incomplete

excision of the tumor with the adherent skin be done without any attempt at removal of breast or lymph glands. The operation should then be followed by surface application of radium. The palliative operation was performed and no attempt was made to remove the tumor completely, the skin, however, was excised widely, sutured, and healed by primary union. Under subsequent radium treatment the remnants of the tumor in the breast diminished in size and the gland in the axilla disappeared. It is nearly two years since the operation, and the patient is free of any local or general disturbance.

The writer has had occasion to observe so many hopeless cases of cancer in which an error not only in the diagnosis but also in the method of treatment was made previous to their entering the cancer division of the Montefiore Hospital that it was thought that it would increase the efficiency of the service of the institution to the community by organizing a *clinic for diagnosis and treatment of early cases of cancer*. This clinic is equipped with radium emanation laboratories, high-voltage X-ray therapy apparatus, and is assisted by all the facilities of the surgical and all other divisions of the hospital.

A *group study* is thus established in the clinic of the complex diagnostic and therapeutic problems of cancer, which is in the opinion of the writer the only method of approaching the subject. Cancer research today needs co-operation of physicists, chemists, pathologists, biologists and clinicians of all specialties in medicine and only teamwork may accomplish results.



# Action of Radium and Roentgen Rays on Normal and Diseased Lymphoid Tissue

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NEW YORK

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# ACTION OF RADIUM AND ROENTGEN RAYS ON NORMAL AND DISEASED LYMPHOID TISSUE\*

ISAAC LEVIN, M.D.

NEW YORK

My associates and I have ascertained in a series of clinical and experimental investigations that the lymphocytes circulating in the blood are most readily influenced by radium and roentgen rays, while all the other normal types of leukocytes and the erythrocytes possess a greater resistance. Normal blood of a turtle contains from 3 to 10 per cent. of polymorphonuclear leukocytes and from 97 to 90 per cent. of lymphocytes. After radiation the relative amounts of the two types of white cells in the blood of the turtle change so that the polymorphonuclears appear in about 80 per cent., as against 20 per cent. of the lymphocytes. The normal blood of a frog contains from 10 to 20 per cent. of polymorphonuclear leukocytes and about 80 per cent. of lymphocytes. After irradiation the numerical proportion changes so that the number of polymorphonuclears in the frog equals from 70 to 80 per cent., and of the lymphocytes from 30 to 40 per cent. The following phenomenon observed in the course of this investigation supports strikingly the conception of the specific action of the rays.

The experiments consisted in the injection of an emulsion of yeast into a normal frog, which was followed twenty-four hours later by irradiation of the animal with roentgen rays or by an insertion of a radium emanation capillary into the dorsal lymph sac of the frog. The injection of yeast is followed by a change in the blood of a frog similar to the one induced by the roentgen rays or radium. The change is most marked twenty-four hours after the injection and

\* From the Department of Cancer Research, Montefiore Hospital.

\* Read before the Section on Pathology and Physiology at the Seventy-Second Annual Session of the American Medical Association, Boston, June, 1921.

continues for a few days. Neither the roentgen rays nor the radium produced any further noticeable change in the numerical relationship between the lymphocytes and the polymorphonuclear leukocytes of the yeasted frogs. At the most, a slight additional decrease of the lymphocytes takes place. Evidently the polymorphonuclear leukocytes resist the action of the rays even when their relative number in the blood is increased.

The total count of the white cells of the frogs was practically unaffected either by the radiations or by yeasting. Apparently the mechanism of the action of the rays on the leukocytes of the blood consists in the destruction of the lymphocytes, which is then followed by the release of the polymorphonuclear leukocytes from the depots in the bone marrow or by an overproduction of this type of cells by the blood-forming organs.

Certain investigators maintain that the polymorphonuclear leukocytes are most readily destroyed by the rays. However, the analysis of their results shows that the destruction of the polymorphonuclear leukocytes is caused by the action of a lethal dose of the rays which produces a severe lethal leukopenia. Zoellner,<sup>1</sup> for instance, reports that the polymorphonuclear leukocytes are most severely affected, while the perusal of his experiments shows the following results: The blood of a normal guinea-pig contained 15 per cent. polymorphonuclears and 85 per cent. lymphocytes. Two days after irradiation the blood showed 54 per cent. polymorphonuclears and 46 per cent. lymphocytes; three days after irradiation, 76 per cent. polymorphonuclears and 24 per cent. lymphocytes. Near death there developed a severe leukopenia of from 12,000 to about 600 white cells, and then the whole blood smear may show only one or two lymphocytes and no polymorphonuclear leukocytes.

As a general rule, as stated above, in all the animals tested as well as in the human being, the lymphocytes are most severely affected and readily destroyed by the irradiations.

The specific radiosensibility of lymphocytes explains the action of radium and roentgen rays on normal and

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1. Zoellner: *Strahlentherapie* 9: 607, 1919.

diseased lymphoid tissue. Intense irradiation of any region of the organism and not the direct raying of lymphoid organs is followed by a complete or partial destruction of the cellular elements of lymphoid tissues—the cells of the medullary part of the lymphatic glands, the malpighian corpuscles of the spleen, Peyer's patches of the intestines, the tonsils and the thymus gland of children. This destruction of the lymphocytes within the lymphoid tissue is accompanied by endarteritic obliteration of blood vessels and formation of dense connective tissue.

Normal lymphoid tissue is comparatively less radiosensitive than the various types of hyperplasias of lymphoid tissue. Furthermore, simple inflammatory hyperplasias are less radiosensitive than the neoplastic hyperplasias. It is comparatively difficult to influence with radium and roentgen rays bacillary infectious lymphomas like the tuberculous glands. Favorable reports were published recently of results of radium and roentgen-ray treatment of infected tonsils. I am investigating the subject in a series of cases. The investigation is not yet completed, and the results of the study will be reported later.

Hodgkin's disease morphologically and etiologically must be classified with the infectious lymphomas. However, it presents a type of actively proliferating neoplastic hyperplasia of the lymphoid tissue and is extremely radiosensitive. Under the influence of radium and roentgen rays there takes place in a Hodgkin's lymphatic gland necrotization of lymphoid tissue accompanied by hemorrhages, proliferative endarteritis of the arteries, and ultimately replacement of the lymphoid cellular structures by dense connective tissue. Later on, part of this newly formed connective tissue is also absorbed and there is only a minute hard nodule left of the affected lymphatic gland. Frequently the gland disappears entirely. A similar process takes place within an enlarged spleen, when it shrinks to normal size under the influence of radium or roentgen rays. Microscopic examination of the spleen of a rabbit into which a radium emanation capillary was placed a week before the removal of the spleen disclosed necrosis of the lymphoid tissue and thickened walls of blood vessels.

Lymphosarcoma, which presents a true neoplasia of lymphoid tissue, is influenced by irradiation more promptly and completely than any other type of lymphoid hyperplasia. Thus, beginning with normal lymphocytes circulating in the blood and ending with lymphosarcoma, all types of normal and diseased lymphoid tissues are influenced more or less promptly by radium and roentgen rays.

In the following parts of this presentation a more detailed discussion will take place of the mechanism of the action of these agents on the various diseases of the lymphoid tissue.

#### STATUS THYMICOLYMPHATICUS

This disease of childhood consists of general lymphoid hyperplasia. The most important manifestation is the enlargement of the thymus, which causes frequent attacks of so-called thymic asthma. These attacks frequently cause sudden death of the patient. In Case 1, status thymicolymphaticus with frequent attacks of thymic apnea, the patient was apparently cured by radium and roentgen rays:

CASE 1.—G. M. A., boy, aged  $3\frac{1}{2}$  years, a gracile, handsome child, whose parents and a little sister were normal, on Dec. 27, 1918, had the first attack of thymic asthma and a second attack ten days later. The next day enlarged tonsils were removed, and a roentgenogram of the chest (Fig. 1) revealed an enlarged thymus. The plate showed the characteristic convex line of the thymic shadow passing into the cardiac shadow. Jan. 15, 1919, radium and roentgen-ray treatment of the region of the thymus was begun. During the treatment the child had attacks once in ten days, then at irregular intervals. The last attack took place, July 18, 1919. A roentgenogram (Fig. 2) taken one and a half years after the beginning of the treatment revealed a small thymic shadow with concave lines as it passed into the cardiac shadow. At present, two and a half years after the beginning of the treatment, the boy is strong and virile and has lost the gracile type of beauty characteristic of status thymicolymphaticus.

As stated above, the disease is caused not only by thymic enlargement but also by general lymphoid hyperplasia. The most important feature in this case is that there undoubtedly has taken place under the influence of the irradiations a correction of the whole

lymphoid system of the organism, and the treatment was given only to the region of the thymus. This phenomenon will be discussed in more detail later.

#### HODGKIN'S DISEASE AND MEDIASTINAL TUMOR

As stated above, Hodgkin's disease is etiologically considered an infectious lymphoma. Nevertheless the main features of the disease set it apart from any known inflammatory disease of lymphoid tissue. Micro-



Fig. 1 (Case 1).—Before treatment: enlarged thymus.

scopically, the main feature of Hodgkin's granuloma is not a degenerative process, as in syphilis or tuberculosis, but an active proliferation of all types of cells of the lymph gland. This proliferation is limitless and ends only with the death of the organism, and therefore every cell within a Hodgkin's granuloma is biologically identical with a cancer cell. The disease is very promptly influenced by radium and roentgen rays. The opinion prevails that the action of the rays is only palliative and that ultimately the patients fail to respond to treatment. These unsatisfactor results

are probably due to the fact that treatment is attempted only late in the course of the disease and is not pursued with sufficient energy. In several early cases I succeeded in arresting the disease for from six to eight years, which is a longer period than the patients usually remain alive untreated. The following is a case in point:

CASE 2.—Miss M. P., aged 20, a professional ballet dancer, came to me six years ago. The swelling in the right side of the neck (Fig. 3) was noticed two months previously and

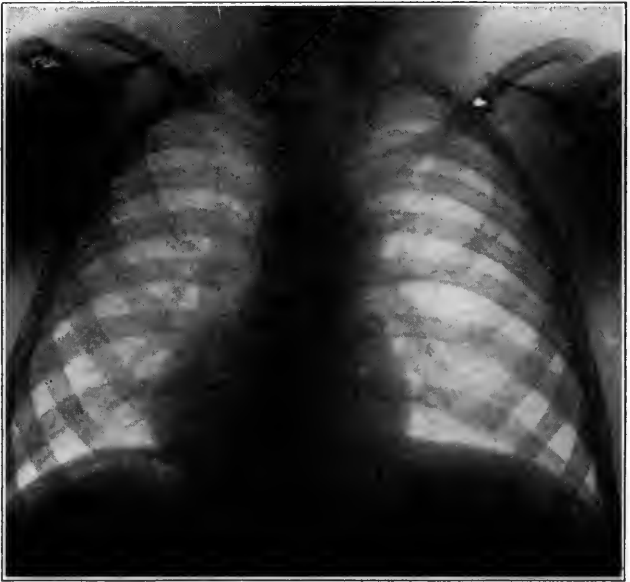


Fig. 2 (Case 1).—After treatment: thymus normal.

rapidly grew to the size noted in the photograph. The patient felt weak and had occasional attacks of fever. The state of her general health and the deformity made it impossible for her to continue her work. Examination revealed that the swelling was due to a packet of enlarged lymphatic glands of various sizes. There were no enlarged glands anywhere else. The spleen and the liver also were not enlarged. The patient received radium applications to the glands of the neck and no other treatment. Six weeks later the swelling completely disappeared, the shape of the neck became normal, and the patient went back on the stage. The treatment was continued for some time, and at present the patient is well and continues her professional occupation.

Mediastinal tumor presents the most distressing and clinically severe type of Hodgkin's disease. The promptness with which these massive tumors disappear under treatment is possibly the best evidence of the great radiosensitiveness of diseased lymphoid tissue. Case 3 may serve as an illustration:

CASE 3.—M. J. H., a man, aged 24, sent to me for treatment in June, 1920, noticed swelling of the glands of his neck in 1918. The examination revealed enlarged lymphatic glands on both sides of the neck and in both axillary regions, and a



Fig. 3 (Case 2).—Tumor of the neck, Hodgkin's disease.

diffuse bulging in the upper sternal region. Roentgen-ray examination disclosed a bulky diffuse tumor in the mediastinum. The patient received both radium and roentgen-ray treatment which were directed to the mediastinum, both cervical and axillary regions. The last examination in May, 1921, showed the mediastinal tumor to have been reduced considerably in size; the lymphatic glands are not palpable, the bulging in the sternal region has disappeared. The patient lost the respiratory mediastinal distress and is clinically well.

## LYMPHOSARCOMA AND LYMPHATIC LEUKEMIA

Both lymphosarcoma and lymphatic leukemia are malignant diseases of the lymphoid tissue which manifest themselves with rapid and continuous proliferation of lymphocytes. There is a great deal of kinship between these two diseases and Hodgkin's granuloma. In fact, there is a great deal more of a clinical difference between lymphosarcoma on one hand, and lymphatic leukemia on the other, than there is between either of the two and Hodgkin's. Lymphosarcoma is a more localized disease than Hodgkin's, while lymphatic leukemia is more generalized than Hodgkins. A number of authors maintain that the difference between the three diseases is rather one of degree than of kind. In any event, this is absolutely correct as far as the therapeutic action of radium and roentgen rays is concerned. All the three diseases give excellent immediate clinical results. The ultimate results are even possibly better in lymphosarcoma than in Hodgkin's, since in the former generalization does not take place as readily as in the latter. The ultimate results in lymphatic leukemia, on the other hand, are worse than either in Hodgkin's or in lymphosarcoma. This difference is probably due to the fact that leukemia is a systemic generalized disease from its incipience.

However, radium and roentgen rays do not act in diseases of the lymphoid tissue as a purely local agent. A local application of radium to one region seems to influence the whole systemic abnormality. Cases 4 and 5 will illustrate this phenomenon:

CASE 4.—Mr. I. H., aged 62, developed a mass in the right axilla, which was removed surgically. Microscopic examination showed it to be lymphosarcoma. The condition recurred in six weeks, and the patient was then referred to me for radium treatment. The examination revealed a large diffuse mass, about the size of a grapefruit, occupying the whole of the axilla and invading the pectoral muscles. In the left axilla there was found an enlarged, freely movable gland the size of a hen's egg. The radium applications were made only at the right axilla, but with complete disappearance of the tumor in the right axilla the enlarged gland in the left axilla also disappeared. I have noted the same phenomenon in other cases.

CASE 5.—Mrs. R. A., aged 60, referred to me for radium and roentgen-ray treatment for a condition of lymphatic leukemia in October, 1920, suffered from diarrhea for two



years and noticed the enlarged glands a year before the beginning of the treatment. Examination revealed lymphatic enlargement everywhere, the spleen reaching to 2 inches below the umbilicus and the free border of the liver reaching to the umbilical line. The blood showed a total white count of 184,000. The differential count revealed 89 per cent. of small lymphocytes. The radium and roentgen-ray treatment was given to the region of the spleen. The treatment was followed not only by diminution in the size of the spleen but also by an improvement of the blood picture and by the practical disappearance of all the enlarged lymph glands. The diarrhea, however, is as distressing as it was at the beginning of the treatment, and the general weakness still persists. None the less, the general effect on the whole lymphoid system of local applications of radium to the area of the spleen is remarkable.

#### MYELOID LEUKEMIA

It was stated above that the polymorphonuclear leukocytes are not radiosensitive. <sup>12</sup> have shown in a previous publication that myelocytes in conditions other than myeloid leukemia are also not radiosensitive. The myelocytes of myeloid leukemia which are so readily destroyed by radium and the roentgen rays must represent biologically a different type of a cell more akin to a cancer cell. The disease responds very promptly to irradiation, and again the remarkable fact is that local irradiation of the spleen changes the picture of the blood, though the myelocytes are derived mainly from the bone marrow.

CASE 6.—Mr. W. P., aged 42, was referred to me in September, 1920, for radium treatment of a condition of myeloid leukemia. Examination showed the spleen reaching to about 1 inch above the umbilicus, and no enlargement of lymphatic glands or liver. Blood examination made before beginning of treatment gave a total count of 220,000 leukocytes. The differential count was: polymorphonuclears, 63 per cent.; lymphocytes, 2 per cent.; myelocytes, 31 per cent.; eosinophils, 1 per cent.; mast cells, 3 per cent. Examination of the patient in March, 1921, seven months after beginning of the treatment, revealed the spleen not palpable; leukocytes, 22,000; polymorphonuclears, 75 per cent.; small lymphocytes, 17 per cent.; myelocytes, 5 per cent.; eosinophils, 1 per cent.; mast cells, 2 per cent. The treatment consisted in local application of radium and roentgen-ray treatment of the region of the spleen. The general condition and strength of the patient improved remarkably.

## PERNICIOUS ANEMIA

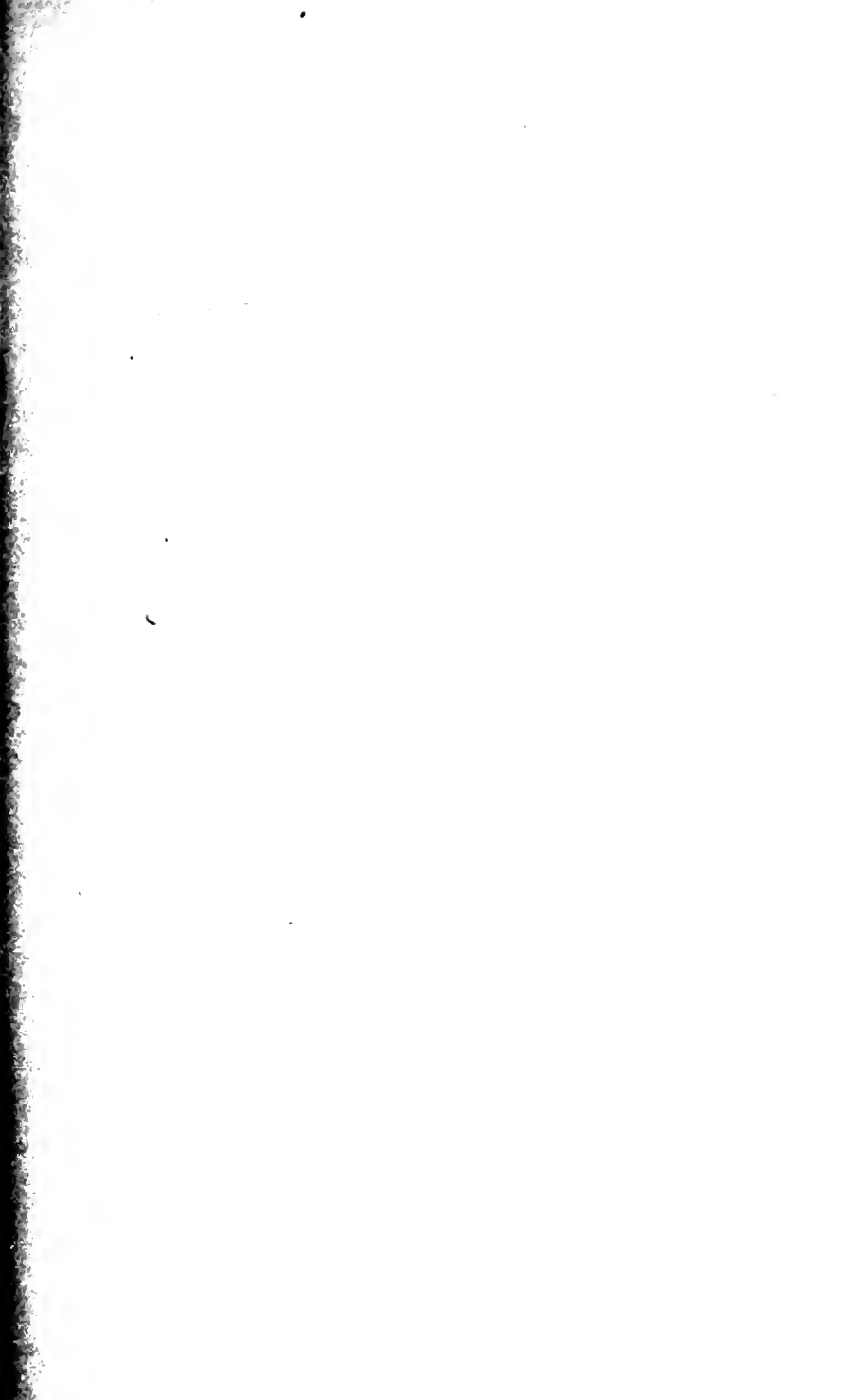
Several English and German authors reported good results from treatment of cases of pernicious anemia with irradiations. In view of the fact noted above that radiation of the spleen influences favorably the course of various diseases of blood and lymphoid tissue, and the further fact that splenectomies are attempted for the cure of pernicious anemia, I decided to investigate what influence radiation of the spleen would have on the course of pernicious anemia. Two cases were selected with a perfect blood picture of a severe pernicious anemia and a large spleen. Since the hemoglobin showed 20 per cent., transfusions were done in both cases and radium was applied to the spleen once a week. There has taken place in both cases a general clinical improvement of the blood picture. It is impossible to ascribe this clinical improvement to the action of radium, since transfusion alone may temporarily improve the condition of the patient. Moreover, spontaneous remissions frequently take place in the course of the disease. It is remarkable, however, that in both patients the clinical improvement was accompanied by a return of the spleen to a normal size. This shrinking of the enlarged spleen could be caused only by the radium treatment, and there is a good deal of evidence to prove that the destruction of the erythrocytes in pernicious anemia takes place in the spleen. It would seem to me that the subject is worthy of further study.

## CONCLUSION

The outstanding feature of the present investigation consists in the fact which it brings forward that, in diseases of the lymphoid tissue, radium and the roentgen rays do not act merely as a local agent which reduces the size of a tumor or an organ, but produce a generalized effect on the lymphoid system of the whole organism. It is impossible to assert at present with any amount of certainty what the mechanism of this influence is. Some investigators maintain that specific enzymes are freed from the desintegrating lymphocytes. The hypothesis is quite plausible, but there is hardly any work done yet to clear up the problem.

Lymphoid tissue in health and disease is of greatest importance in animal economy, and the action of radium and roentgen rays on this tissue presents the most remarkable phenomenon in biology. Experimental and clinical study of the problem will elucidate, on the one hand, the mechanism of the biologic action of the rays generally, and will also help in clarifying many mooted problems of structure, derivation and pathogenesis of the blood, blood-forming organs and lymphoid tissue both normal and diseased.







## Studies on plant cancers—I. The mechanism of the formation of the leafy crown gall\*

MICHAEL LEVINE

(WITH PLATES 17 AND 18)

Smith in 1916 (1) announced a new type of crown gall, consisting of leafy shoots, which was produced by inoculating the leaf axils of a plant, where a dormant bud was present, with *Bacterium tumefaciens*. Similar leafy crown galls were produced by inoculating the midvein of the leaf of the tobacco, with the bacterial organism. Smith considered this type of crown gall identical with the atypical teratoid embryomata found in the animal. In 1917 (2) he showed further evidence of the power of this organism to produce leafy shoots in fifteen different families of plants. He contends that the leafy tumor is produced by inoculating *Bacterium tumefaciens* into the tissue of a susceptible species in the vicinity of totipotent cells.

Levin and Levine in 1918 (3) indicated that these leafy shoots are always secondary and that the crown gall develops first and then a group of crown gall cells become differentiated and give rise to a tissue, an organ, or potentially an entire plant, the leafy shoot. According to these authors, such differentiation of cells of a malignant tumor does not occur in animal cancer. Crown gall represents only one type in the large group of pathological processes known under the general term "cancer."

It occurred to the writer that if, as Smith claims, *Bacterium tumefaciens* inoculated into the epidermis (epithelium) of a plant gives rise to an epithelioma and a similar inoculation into the cortex or vascular bundles (connective tissue) produces a sarcoma, then the inoculation of a plant in any region of totipotent cells (bud Anlage), which are known to produce leafy shoots under normal conditions should produce them under the added stimulus of *Bacterium tumefaciens* much more readily and in greater abundance.

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\* From the Department of Cancer Research of the Montefiore Hospital, New York, Dr. Isaac Levin, Chief.

It is well known that when *Bryophyllum calycinum* leaves are detached from the mother plant and are put on moist soil the marginal notches of the leaves, at which totipotent cells are found, develop into leafy shoots and eventually form new plants. For this reason, leaves and stems of *B. calycinum* were used to study the effect of the bacterium on the leafy shoot formation.

#### METHOD OF MATERIAL

The leaves of *B. calycinum* were detached from the plant and were placed on moist soil in pots in the greenhouse. The marginal notches of one side of the leaf, right or left, upper or lower, were inoculated, by pricking the tissue five to ten times with a delicate needle containing a culture of *Bacterium tumefaciens* from five to forty days old. The uninoculated notches of the opposite side of the leaf, served as controls, after they had been pricked with a sterile needle. Entire leaves with each notch pricked five to ten times with a sterile needle were also used as controls. Leaves in all stages of development were used. The veins of leaves and growing regions of stems of the *Bryophyllum* were also inoculated with *Bacterium tumefaciens*. In all over a thousand inoculations were made. It may be stated that thin young leaves did not lend themselves to these experiments, because they dried out too rapidly. It was likewise found that normal embryos develop better in the greenhouse than in the open.

As a rule, two days after inoculation with *Bacterium tumefaciens* both the infected and control notches showed necrotic areas in those regions. It appeared, however, that the wounds infected showed greater areas of dead tissue, which subsequently caused deeper indentations at the margin of the leaf. This was also observed by Levin and Levine (3) for a number of plants. The uninfected or control notches recovered readily and although slight scars were formed, the bud Anlagen in the notches developed into normal embryos forty to seventy days after injury. Inoculations were made: (1) into the notches of *Bryophyllum calycinum* leaves; (2) into the leaf in the vicinity of the notches; (3) into the midveins of the leaf; and (4) into the growing regions of the young stems of this plant.



## OBSERVATIONS

1. *Inoculation of Bacterium tumefaciens into the notches of Bryophyllum calycinum leaves*

The study of this material shows that in the great majority of cases, the notches infected with *Bacterium tumefaciens*, instead of causing the development of leafy shoots, formed ordinary crown galls. FIG. 1 represents a young detached leaf forty-five days after having been placed on soil and having had the basal notches inoculated with the bacterium. The apical notches were pricked with a sterile needle and served as controls. The inoculated notches show well-developed ordinary crown galls without leafy shoots, while the control notches on the ventral surface show the beginning of the development of leafy shoots.

FIG. 2 represents an older leaf, in which the basal notches were inoculated forty-five days previously. In this case no galls or shoots have as yet been formed at the notches but the control notches are beginning to proliferate and the uppermost notch of the leaf has produced a shoot. FIGS. 3 and 4 represent the ventral and dorsal surfaces of a detached leaf seventy days after inoculating the basal notches with the bacterium. All the basal, infected notches show well-developed galls without leafy shoots on the ventral surface (FIG. 3). The majority of the control, apical notches have already developed leafy shoots. FIG. 5 represents an old detached leaf grown on soil, 140 days after the basal notches were infected. The mother leaf is seen in the center of the figure with a number of well-developed shoots coming from the apical notches. The basal, inoculated notches all show well-developed crown galls. In one instance a poorly developed shoot, visible in FIG. 5 over the largest gall, made its appearance. A similar condition is shown in FIG. 7. These leafy shoots appeared much later in the development of the gall. This seems to show the dwarfing and inhibiting effect the crown gall organism has on the growth of the bud Anlage.

2. *Inoculation in the vicinity of the notch*

When the inoculation is made near the notch instead of in it, a crown gall is developed alongside of a poorly developed leafy

shoot. This is shown in FIG. 6, which represents a leaf forty-five days after inoculation with *Bacterium tumefaciens*. The control notch developed a much larger and more vigorous leafy shoot.

FIG. 7 represents an old detached leaf, 140 days after inoculation. Here again several of the inoculations were made near the bud Anlagen. To the left are seen the large plants which have developed from the control notches. At the right, in the foreground, are seen three galls; next to the lower ones there appear small dwarfed plants. It appears that the galls have interfered with the normal development of these leafy shoots when compared with the large normal plants seen to the left.

### 3. *Inoculation in the midvein*

It may be assumed that the midvein may have totipotent cells which by the inoculation of *Bacterium tumefaciens* can be stimulated to develop leafy shoots. Forty leaves of *B. calycinum*, both young and old, detached from and attached to the mother plants, were inoculated with *Bacterium tumefaciens* by means of pricking the midvein of the leaf with a fine needle. All produced crown galls within a month after the inoculation. FIGS. 2 and 3 show the appearance of such galls on young leaves forty days after the inoculations were made. FIG. 8 represents an old leaf attached to the mother plant. A large gall has been formed on the midvein by inoculating it with the bacterium five months previously. The tumor is a characteristic crown gall consisting of a great number of tubercles. This leaf was carefully guarded in the hopes that these tubercles would produce leafy shoots. FIG. 9 represents the gall shown in FIG. 8, nine months after inoculation. The leaf became detached and withered. The gall has grown considerably larger, taking on a cylindrical shape, and has become covered with numerous tuberosities. No leafy shoots were formed.

### 4. *Inoculation of the growing region of the stem*

A large number of *B. calycinum* plants were also inoculated with *Bacterium tumefaciens* in the growing region of the stem with the object of stimulating there the possible totipotent cells to leafy shoot formation. FIG. 10 (a, b, c, e, f) represents a few of the

young plants in which the growing regions had been inoculated four months previously. In one case only has a small leafy shoot been formed (FIG. 10, *b*). This, however, appeared after the crown gall had been well established. The plants are all dwarfed, as may be seen by comparing FIG. 10, *a*, *b*, *c*, *e*, and *f*, with *d*, one of the control plants.

#### SUMMARY AND CONCLUSIONS

1. *Bacterium tumefaciens* inoculated by pricks of a delicate needle into the marginal notches of a leaf of *Bryophyllum calycinum*, where totipotent cells are present, results in the formation of a crown gall as readily as in other plants used for inoculation but without leafy shoots.

2. Inoculation of *Bacterium tumefaciens* into the tissue of a leaf of *B. calycinum* in the vicinity of a small bud causes the formation of a gall and interferes with the normal development of the bud or leafy shoot.

3. Inoculation of *Bacterium tumefaciens* into the midvein of a young or old leaf detached from or attached to the mother plant results in the development of a large gall without the development of leafy shoots.

4. Inoculation of *Bacterium tumefaciens* into the growing region of the stem of a young plant causes the development of the ordinary crown gall with the occasional and subsequent development of a leafy shoot.

5. *Bacterium tumefaciens* does not cause the formation of leafy shoots in *Bryophyllum calycinum* but rather inhibits and retards their normal development, when inoculated into the totipotent cells which appear at the notches of the leaf.

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## Description of plates 17 and 18

## PLATE 17

FIG. 1. Young leaf of *Bryophyllum calycinum*, showing well-developed crown galls at the basal notches, inoculated with *Bacterium tumefaciens* forty-five days previously.

FIG. 2. Older leaf, control notches showing leafy shoots, none appearing at the inoculated notches forty-five days later. The midvein, also inoculated, shows ordinary crown gall.

FIGS. 3, 4. Ventral and dorsal surfaces of a leaf, the basal notches and midvein of which were inoculated with *Bacterium tumefaciens*, showing well-developed galls without leafy shoots. The control, apical notches show normal leafy shoots.

FIG. 6. Young leaf, in which the inoculations were made near the apical notches, showing a dwarfed leafy shoot with a crown gall attached to it. One of the control notches shows a well developed leafy shoot.

FIG. 10. Young plants. In *a*, *b*, *c*, *e*, and *f*, the growing regions were inoculated; in *d*, there was no inoculation.

## PLATE 18

FIG. 5. Old leaf, inoculated at the basal notches 140 days previously, showing a large crown gall. The control notches show normally developed plants coming from them.

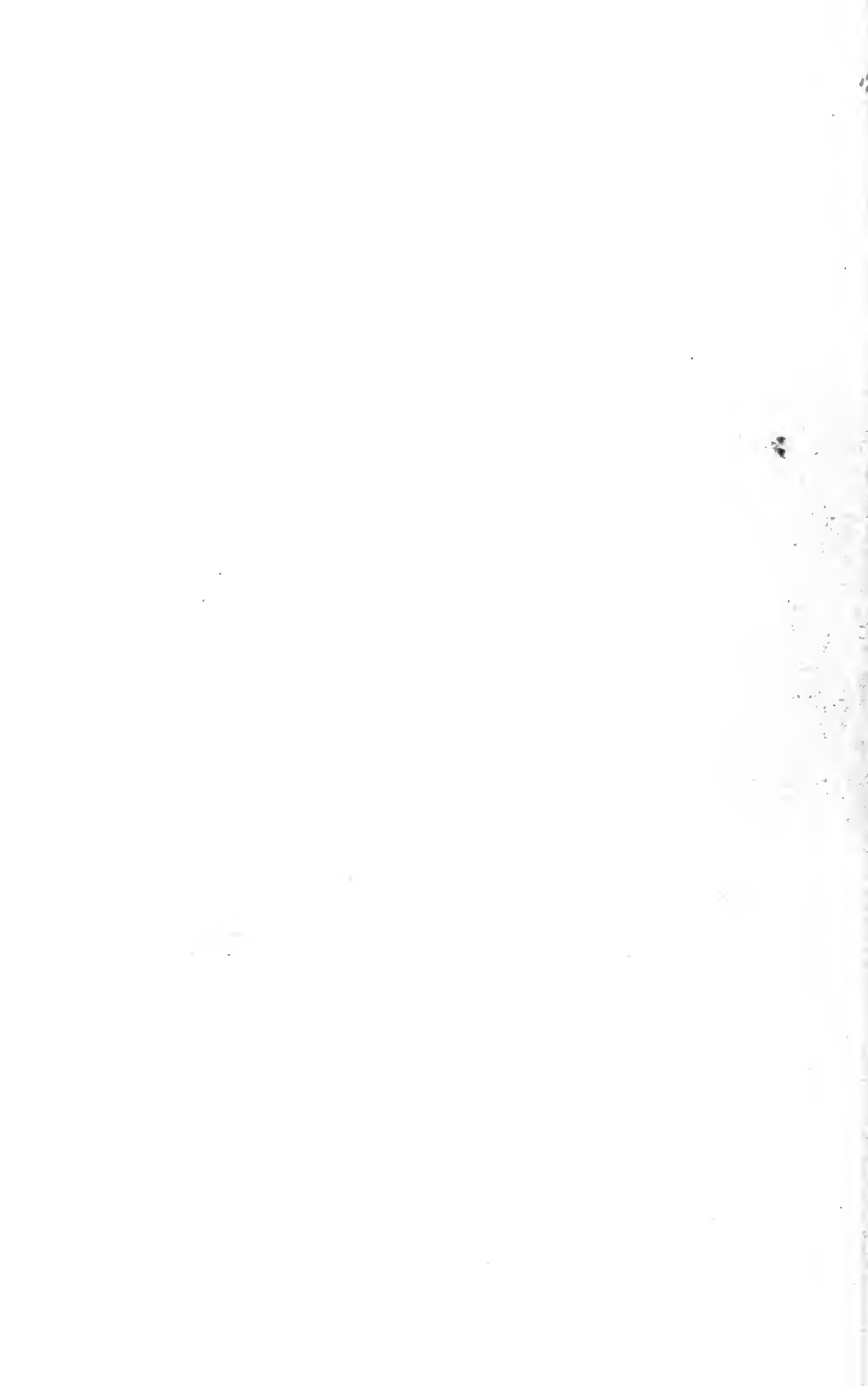
FIG. 7. Old leaf, 140 days after inoculations were made near the notches, showing dwarfed leafy shoots growing in contact with crown galls. The control notches have developed normal plants.

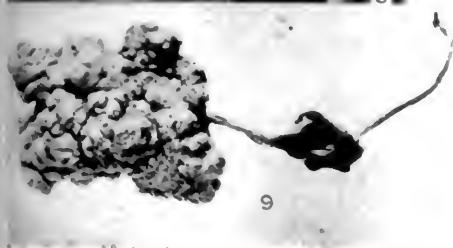
FIG. 8. Old leaf attached to mother plant, showing a large gall on the midvein produced by inoculating it with *Bacterium tumefaciens* five months previously.

FIG. 9. Same leaf now detached, nine months after inoculation.



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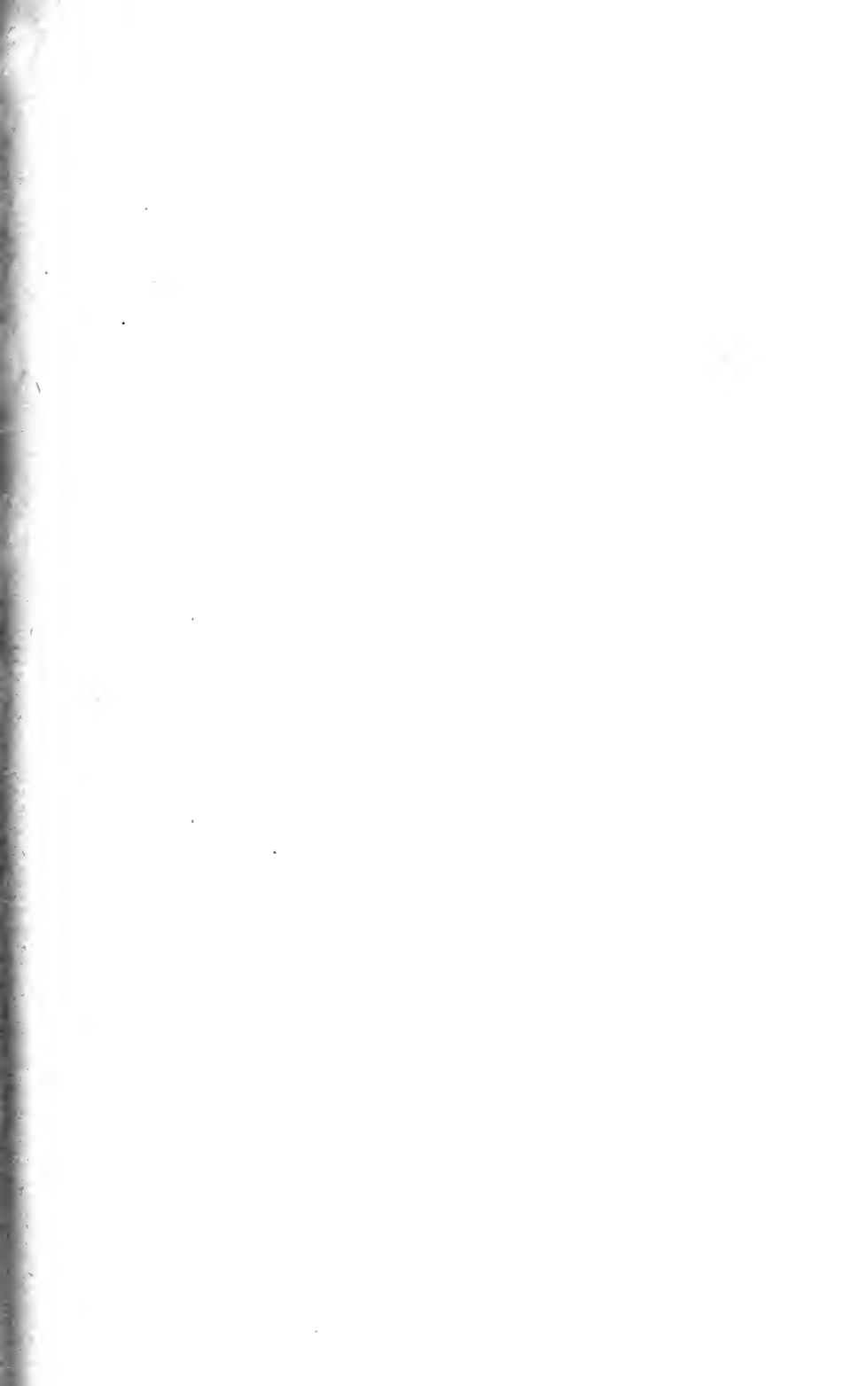


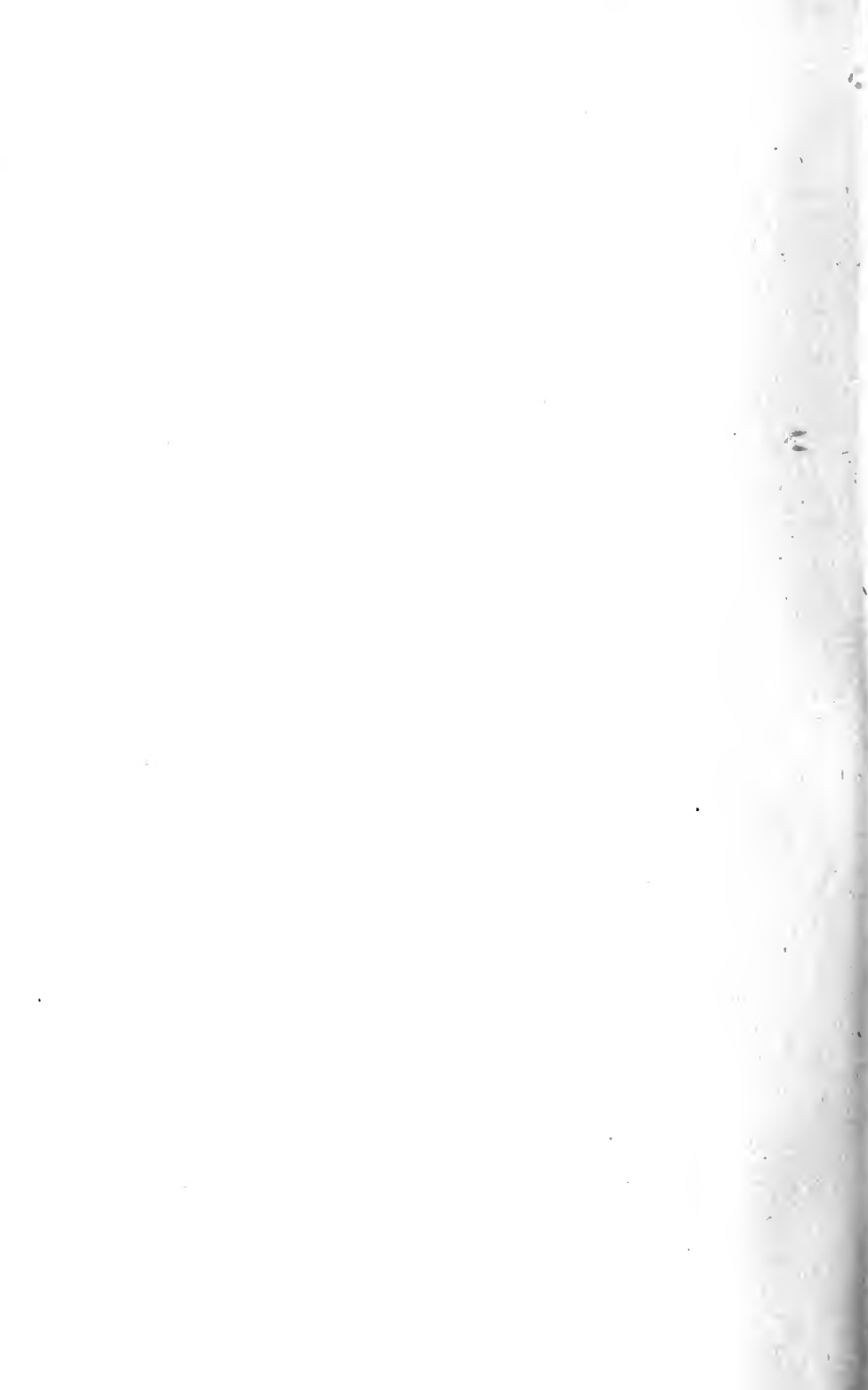


LEVINE: PLANT CANCERS









## STUDIES ON PLANT CANCERS—II

### THE BEHAVIOR OF CROWN GALL ON THE RUBBER PLANT (*FICUS ELASTICA*)<sup>1</sup>

(WITH PLATES 1 AND 2)

MICHAEL LEVINE

Toumey (1900) in studying the effects of crown gall on the host pointed out the destructiveness of this disease on deciduous trees. He gave an adequate picture of the developmental stages in the growth of the crown gall tissue on the almond. He contends that the period of growth of the crown gall is definite and usually extends over the growing season; after which time the gall dies, falls out, leaving an open wound. In the following spring a new crown gall is formed on the margin of the old wound which in turn dies and increases the area of the lesion, so that it weakens the tree and causes it to break off in a wind, thus killing it. It appears from Toumey's study that death is the result of a mechanical effect of the crown gall on the tissue of the host in no way similar to the toxic effects that the cancerous growth has on the animal or human being.

Hedgcock (1910<sup>1</sup>) in his field studies of the effect of crown gall on grape showed that the crown gall stunts the plant and that when the galls occur on the stem under the ground they commonly decay, killing the adjacent tissue and often killing the vine above the point of attack. Whether the decay is directly brought

<sup>1</sup> From the Cancer Research Laboratory, Montefiore Hospital, Dr. Isaac Levin, Chief. The first paper was published in Bull. Torrey Club 46: 447-452, pls. 17, 18. 1919.

about by *Bacterium tumefaciens* Hedgcock does not state. He claims however with Toumey that the galls die annually. In a later study (1910<sup>2</sup>) of crown gall on the apple he maintains that the destructive effect of this disease is overrated.

Smith (1911-12) in his extensive studies on crown gall and its resemblance to animal cancer shows that the physiological effects of these tumors vary from species to species and also within the species and are generally less pronounced and speedy than one might expect. He holds that it is difficult to show conclusively that the substances produced in the tumor by the parasite are absorbed and act as slow poisons. This is especially difficult in view of the fact that the galls are often soaked by rains and become infected with other parasitic and saprophytic organisms.

Levin and Levine (1918-20) in a report on the malignancy of the crown gall and its analogy to human cancer pointed out that a number of the phenomena in both diseases are analogous. They contend that the neoplasms in plants produced by *Bacterium tumefaciens* are sometimes benign though some are true malignant growths. The latter generally dwarf the plant so affected and cause necrosis of the tissue above and below the gall.

These studies and those of Smith's and other workers were carried out in annuals, biennials or deciduous trees in which the period of growth of the host as well as the crown gall is normally interrupted. The difficulty in determining whether toxins are present in such cases is made more difficult by the intervention of natural death, caused by changes in temperature and its concomitant factors, and second, by the occurrence of infections caused by fungi and even insect grubs, the eggs of which are deposited in the soft tissue of the young crown gall.

The purpose of this report is to bring forward further evidence on the malignancy of the crown gall experimentally induced on mature evergreen perennials such as the common rubber tree, *Ficus elastica*. In such plants where the growth is rather active all the year round, when kept under uniform, green house conditions, the effect of the crown gall organism and the neoplastic growth on the host can be kept under observation for an extended period. Drenching rains and destructive insects are

avoided and very often other parasitic and saprophytic fungi. In this way and in such plants as *Ficus elastica* it is possible to show definitely whether and in what degree the crown gall has an injurious effect upon the adjacent normal tissue of the host. It must be remembered however that while transportation of the materials elaborated by the cancer cells of the animal is in some degree limited, this is much more the case in plants.

I have found some evidence of injurious effects spreading from a gall upwards and finally killing the stem above the point of inoculation. This was the result in every case (10 branches) with two exceptions. In the first the signs of death are only now, 14 months after inoculation were made, making their appearance. In the other case described below, the stem, it appears, was cut off for examination too soon.

In no case was there any evidence that the death of the stem above the gall was due to the obstruction of the sap flow or water supply. Toumey's results do not suggest the possibility of any such direct mechanical disturbance on the part of the gall. I will describe briefly a number of cases observed.

*Material and Observations.*—Through the courtesy of Dr. S. Wachsmann, director of the Montefiore Hospital, a number of rubber trees (*Ficus elastica*) were placed at my disposal. These plants were growing in large boxes and were kept indoors during the winter months in a basement room well lighted and ventilated. In the summer these plants were moved out on the campus of the hospital. These plants make almost as much growth during the winter as they do during the summer. Various parts of these plants were inoculated with *Bacterium tumefaciens*, labeled and then examined from time to time. It was found that within a month indications of a crown gall made their appearance in the part of the plant inoculated.

Figure 1 represents one of the trees during the month of January used in this study. The terminal buds are opening and the moderately green glistening apical leaves show evidence of an active condition of growth. The plant shown in figure 1 with five others of equal size were inoculated on July 28, 1919, by pricking the tissue with a steel needle that had been previously

dipped into a culture of *Bacterium tumefaciens*. As few as five pricks of the needles with the crown gall organism were found to be sufficient to produce a visible neoplasm in a month's time. A careful scrutiny of this picture reveals a number of galls at the internodes of several branches (Fig. 1, *a, b*) on the mid-vein of an old leaf (Fig. 1, *c*) and on one of the main branches (Fig. 1, *d*). Where the needle perforated the tissue a crown gall was formed on both sides of the stem or the leaf. No less active were the growths that were produced on the trunk of the tree (Fig. 1, *d*). The galls formed are of the characteristic type described by Toumey, Smith and others. They are always firm, yellowish in color and covered with brownish patches when young and become dark brown in color and of a woody consistency with age, as we shall see below.

The crown gall, at this stage, as far as can be seen, has no specially injurious effect upon the host. The terminal buds of the plant are actively growing and there appears to be no signs of dwarfing of the branches, nor any indication of fasciation of the internodes above the region of inoculation such as those reported by Smith, and Levin and Levine for *Geranium*, *Ricinus*, etc.

Figure 2 represents a branch from another rubber tree which had been inoculated seven months previously on the second internode. The crown gall has grown extensively, covering one half of the circumference of the stem. The surface is dark brown in color, highly convoluted, indicating a number of centers of peripheral growth. The mass is hard and some parts of the surface appear to be dead. The branch however has grown considerably as shown by the number of internodes above the crown gall. (See Figs. 2 and 3.) In June, 1919, it was noted that the terminal bud was small and dark green in color, and showed no signs of growth. This was true of a number of other branches which had been inoculated for the same length of time. The control branches that were similarly treated with a sterile needle had long greenish buds, many of which were opening. This condition suggested at once the possibility of mechanical interference of the crown gall with the water supply of the plant due to partial destruction and possible occlusion of the fibrovascular bundles,

but cross and longitudinal sections of this gall made much later showed this assumption to be incorrect as is further described below. It is obvious at once however that there is some other cause of death than the cutting of the water supply, since in that case, the dying would progress from the tip downward.

*Twelve months after inoculation.* Figure 3 represents the same branch shown in figure 2 on December, 1919, approximately 12 months after the inoculation had been made. The crown gall has almost girdled the stem encircling  $\frac{7}{8}$  of the stem's circumference. The leaves above the crown gall have turned black and fallen off while those below are turning a yellowish brown. The major portion of the stem above the gall is dead, the injury progressing from the gall upward so that at the time the photograph was made the top of the stem (Fig. 3) was still green and showed indications of being alive. A cross section through the middle of this crown gall appears in figure 4 and shows that the crown gall tissue has become fully differentiated and thus further supports the contention of Toumey and Hedgcock that the crown gall growths are annual and Levin and Levine's views that these growths are unlike animal cancers in that they are limited in growth and become differentiated. The wood fibers and parenchymatous cells of which the crown gall is composed are dark brown on the interior of the gall as they are on the surface. The vascular elements are distorted and nodular on the periphery of the tumor where their antecedents were undoubtedly centers of rapid cell division before they became differentiated and old.

Approximately one half of the original cylinder made by the fibrovascular bundles is destroyed and replaced by crown gall tissue. The tissue in the center of the crown gall is dark in color, watery and is apparently disintegrating. The remaining half of the wood cylinder appears to be undistributed and undoubtedly is mechanically fit to carry sap, as evidenced by the still turgid condition of the top of the branch as shown in figure 5. This figure represents a longitudinal section of the upper part of the stem including the upper part of the crown gall. There appears to be only a partial destruction of the wood fibers in the region of the stem occupied by the lesion as seen in the

cross section to the left of the figure. The wood and pith are apparently normal structurally though physiologically dead.

A later state in the necrosis following the inoculation of *Bacterium tumefaciens* is shown in figure 6 photographed eleven months afterward. Here again the inoculation was made at one side of the stem in the third internode with a needle dipped into an emulsion of the crown gall organism. In this late stage the growth does not completely girdle the stem, yet two months previously the leaves fell off and the stem became discolored and finally died. The crown gall and the stem above the gall also died. A short portion of the stem immediately below the gall at the time of the photograph was rapidly undergoing similar changes. The gall in this case again shows all the characteristics of the typical crown galls referred to above. The outer surface is dry and woody and is markedly nodular. In a longitudinal section of this gall we find the region near the stem slightly moist, darker in appearance and invading the wood cylinder (Fig. 7). A large portion of the wood cylinder is intact and appears to be functional. There again, it appears as if death was caused by *Bacterium tumefaciens* or the crown gall cells rather than by the interference with the transportation system caused by the destruction on the invasion of the fibrovascular bundles.

Figure 8 represents a gall 12 months old which has caused no injury to the stem either above or below the gall. Growth is continuing normally. The inoculation was made in two opposite sides of the branch. The crown gall that appears in front on the stem "B" and "C" was produced by inoculating an axillary bud region. The lower gall, "A," was obtained by inoculating an internodal space on the opposite sides of the stem. The lower growth which appears as two separate tumors on opposite sides of the stem consists of one continuous mass of tissue encircling one half of the circumference of the stem. The growth has a distinctly tubercular structure. It is dark brown in color, hard and dry, and apparently dead. The upper crown gall which is on the surface of the stem, as mentioned above, extends for a distance of nearly one half of the circumference of the stem also. To the left it developed into a more or less uniformly globular growth through which two branches have grown.



We may turn now to consider the cases in which no evidence of injurious effects of the gall in tissue above and below it in the stem have yet appeared. In all, I have observed two such cases as mentioned above against ten in which death of the region above and below the gall or both occurred.

It is natural to suspect in view of the statements of the authors quoted that the injurious effects I have observed may be due to the presence of some additional infection or to some special direct physical effect of the crown gall on the rubber tree. I am however convinced that this is not the case.

As in the case of *Bryophyllum* (Levine 1919), *Bacterium tumefaciens* does not cause the formation of eubryomata when inoculated into *F. elastica* in a region where embryonic cells are to be expected. At the time this photograph was made, twelve months after inoculation, the upper gall was still active although parts of it were beginning to disintegrate. The stem above the gall appears as noted to be entirely unaffected and in good physiological condition. A cross section of the stem made at the level indicated by the line "AA" shows complete disorganization of more than one half of the wood cylinder. The remaining half is not unlike the apparently healthy portion of the wood shown in figure 4. A photograph of the cut end of the stem at the level of "BB" (Fig. 8) is shown in figure 9. Here little of the vascular cylinder appears to be invaded by the crown gall tissue. At this level the great mass of the crown gall seems to have developed from the cortical layer of the stem only and has not, at this time, affected the central cylinder.

The gall from which the branches "Y" and "Z" appear (Fig. 9) is unlike all other crown galls so far described in that almost its entire surface is smooth and not tubercular; it is covered with small brown corky patches. The lower left side of the gall in the picture shows the typical crown gall convolutions.

A section still higher up on the stem made at the level indicated by the line "CC" cuts through this smooth gall at a point near the origin of the branches "Y" and "Z" (see Fig. 10). An abundance of milk comes from the entire surface above the dark area of the crown gall shown in this figure. No invasion

of the central cylinder by the crown gall tissue appears. There is, however, a slight hyperplasia of the wood. The fan-shaped vascular elements in the gall seem to be running into the branches "Y" and "Z" from "X." The gall in this case may be compared to the so-called benign tumors (Levin and Levine, 1918). The character of the tissue of this neoplasm does not differ from that of a malignant crown gall. It seems obvious that the death of the crown gall is in general a result of merely mechanical conditions. The gall may be insufficiently supplied with food and water and dies because it fails to establish an adequate connection with the conducting system of the host. It is most likely that this is true of the almond crown gall described by Toumey.

*Bacterium tumefaciens* from stem and crown gall. The possibility that another organism as well as *Bacterium tumefaciens* is present and is responsible for the destruction of the stem apex as shown in figures 3, 5, 6 was tested in the following manner. Small pieces of the interior of the crown gall shown in figures 3 and 6 were carefully removed with a sterile knife and placed in tubes of beef agar. In two days the surfaces of the agar on which the inocula were resting became covered with a hyaline, whitish yellow colored schizomycete which in general appearance is not unlike that of *Bacterium tumefaciens*. Similar results were obtained by planting pieces of the stem from above the crown gall after being superficially sterilized by immersing in a weak formol solution. In all tubes the organisms were more or less alike in their superficial appearance. In several beef agar cultures the hyphae of a mold made their appearance. The presence of the mold we consider accidental contamination. Molds at any rate are not known to be parasitic on and to cause death of the rubber tree.

It appears from this that the organism is carried to parts removed from the gall but owing to its depauperate condition is unable to influence the production of a new growth.

The organism obtained in these cultures were inoculated into the tissue of young growing geranium plants and young shoots of the rubber trees. Crown galls appeared within two months after inoculation. The growths were much smaller than those

obtained by inoculating young geraniums and branches of a rubber tree with a known culture of *Bacterium tumefaciens*. This supports the contention that the bacteria in the distant parts of the stem bearing a crown gall are of a less virulent strain.

#### SUMMARY

1. *Bacterium tumefaciens* inoculated into the apical internode of the branches, into the leaves, or main stem of the rubber tree, *Ficus elastica*, stimulates the development of a neoplasm in the region of inoculation of a benign or malignant nature. The crown galls so formed, in this plant, are of two kinds, one in which growth is uniform and appears to be a swelling, the other is the characteristic convoluted type indicating a peripheral growth of isolated nodules.

2. The early stages in the development of the crown gall in *Ficus elastica* does not interfere with the life of the plant as a whole nor does it interfere with the growth of the inoculated branches.

3. The crown gall in *Ficus elastica* after a number of months of active growth becomes hard and dry and finally dies. This is associated with the differentiation of the tissue which converts the gall into a mass of parenchymatous cells and nodules of woody fibers. The central portion of the crown gall which generally lies near the woody cylinder disintegrates.

4. The invasion of the stem by the new growth does not destroy the entire conducting system of the stem, yet that portion of the stem above the gall dies as well as considerable portion of the stem below.

5. Cultures made from pieces of the crown gall and stem above the gall yield only a schizomycete which in appearance is not unlike *Bacterium tumefaciens* and which when inoculated into the stem of young geranium and rubber plants produce crown galls in the region of inoculation.

6. It is possible that the crown gall cells or the crown gall forming organisms are responsible for the progressive necrosis of the stem from the gall upward and downward. The death of the plant due to crown gall is at least suggestive of the death caused by malignant growths in animals.

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## EXPLANATION OF PLATES 1 AND 2

Fig. 1. Represents the type of *Ficus elastica* used in these experiments. The galls in the various parts of the plant *a, b, c,* and *d* are the result of inoculating them with a culture of *Bacterium tumefaciens*, five months previously.

Fig. 2. Apical portion of a branch showing a large crown gall seven months after inoculation in the second internode. The gall does not seem to have interfered with the growth of the stem; several internodes having been added in the interim. ( $\times \frac{1}{2}$ .)

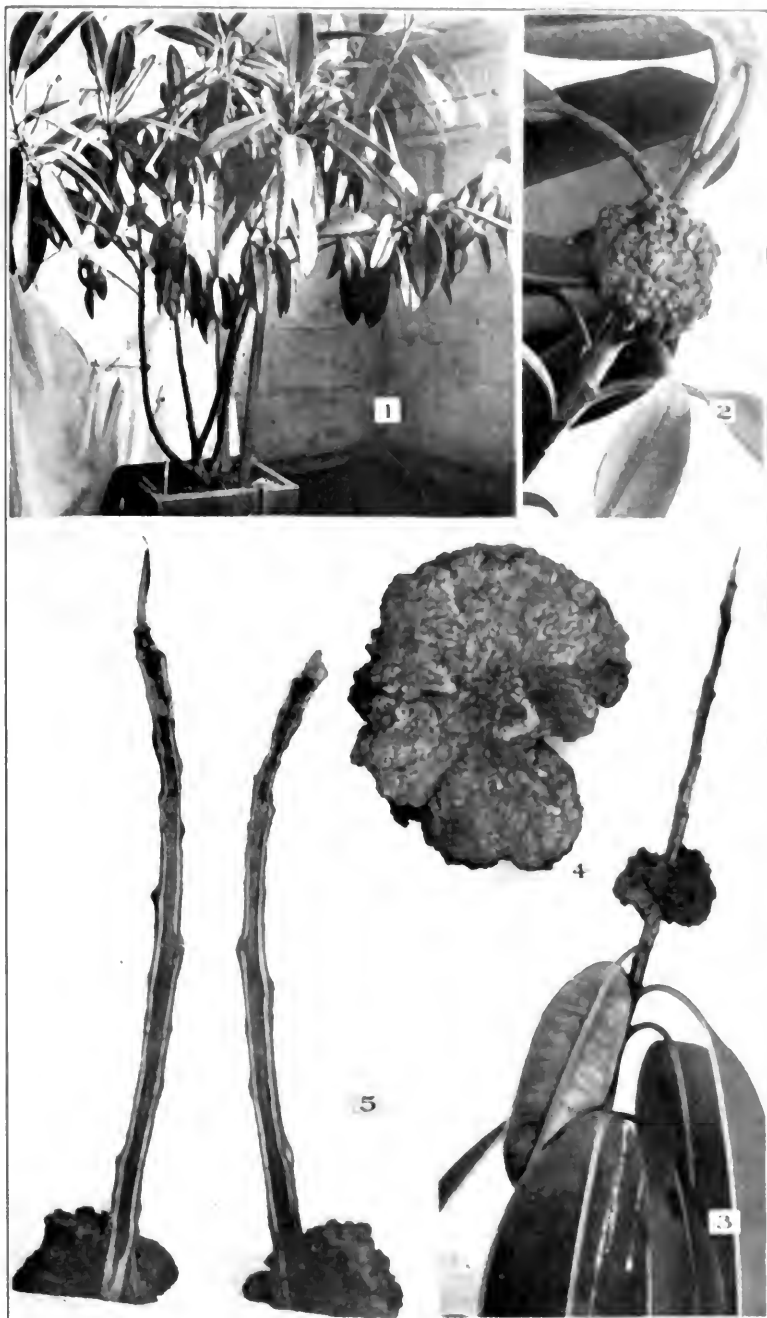
Fig. 3. Same branch twelve months after inoculation. The leaves above the gall have dropped off. The stem is discolored, dry, and dying progressively upward. The tip is still green and alive. The gall is hard, dry and dead. ( $\times \frac{1}{4}$ .)

Fig. 4. Cross section of the stem through the gall shown in figure 3. The wood cylinder is only partially destroyed by the invading gall. The portion of the crown gall near the central cylinder is soft and disintegrating.

Fig. 5. Longitudinal section of the upper portion of the same stem. The portion near the gall is dry, brown and dead, while the apical internode and bud are still green and alive.

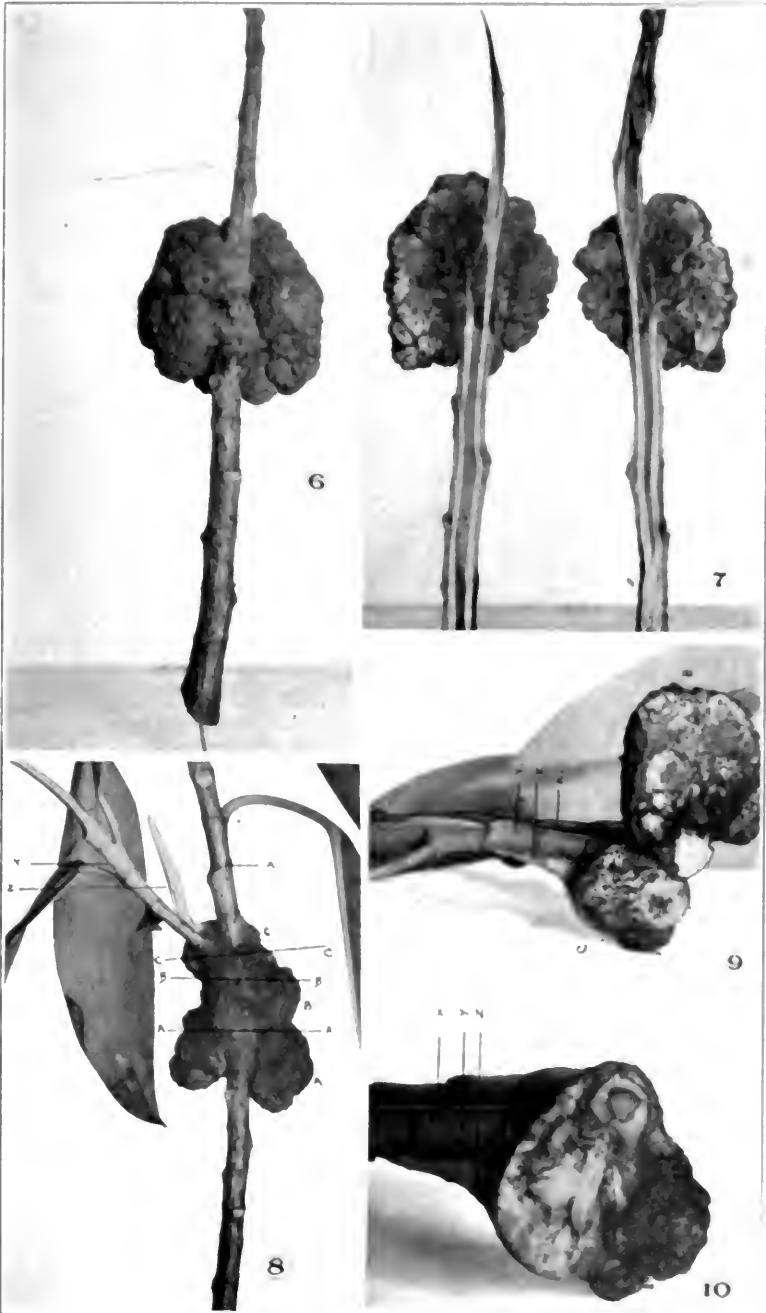
Fig. 6. A branch of *Ficus elastica* in which the gall and the stem above and below the gall is dead; the inoculation having been made twelve months previously.

Fig. 7. Longitudinal section showing invasion of the crown gall destroying a considerable portion of fibrovascular bundles. The invading portion of the gall is soft, spongy and disintegrating.



BACTERIUM TUMEFACIENS ON FICUS ELASTICA





BACTERIUM TUMEFACIENS ON FICUS ELASTICA





Fig. 8. A branch of *Ficus elastica* actively growing twelve months after having been inoculated with *Bacterium tumefaciens*. Two galls formed "A," and "B," "C," on opposite sides of the stem showing the smooth and nodular types of crown galls. Two branches are growing through the smooth crown gall.

Fig. 9. Cross section of stem between the upper and lower crown galls corresponding to level indicated by the line "BB" in figure 8. The gall to the left is of the smooth kind, being covered by corky patches.

Fig. 10. Cross section higher up on the stem corresponding to the level indicated by the line "CC" in figure 8. Shows large brown necrotic area and the undisturbed cylinder of the main stem "X" with bundles of fibers going to branches "Y" and "Z."



STUDIES ON PLANT CANCERS III. THE NATURE OF THE  
SOIL AS A DETERMINING FACTOR IN THE HEALTH  
OF THE BEET, *BETA VULGARIS*, AND ITS  
RELATION TO THE SIZE AND WEIGHT  
OF THE CROWN GALL PRODUCED  
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Little is known concerning either the effect on the size and the weight of beets, either spontaneously or artificially infected with crown gall, or the effect of the general vigor of the plant on its susceptibility to infection. Many problems of practical and theoretical importance along these lines remain to be solved. Among them are: (1) a more accurate evaluation of the effects of the crown-gall disease upon the final size of the infected beet and hence on the beet crop; (2) the cause of the greater susceptibility of the sugar beet as compared with other races to the crown-gall organism; (3) the breeding of beets to obtain strains immune to crown-gall infection and yet retaining the desirable marketable qualities; (4) the cytological difference between crown gall and "tuberculosis" of beets and the relation of the former to animal cancer; (5) the relation of the soil to the health of the beet and to the size of the crown gall that it will harbor when inoculated with *Bacterium tumefaciens*.

Up to the present very little evidence has been advanced by animal pathologists to show any definite relation between the physical condition and the virulence of cancer once it is started.

The purpose of this paper is to present some data on the last of the questions noted above; namely, the relation of the health of the beet to the size of the crown gall resulting from infection. Since the term "health" has but a relative meaning, we shall measure health in this case in terms of size and weight, the matters most important to the beet grower and without doubt fair indices of the vigor and normality of the beet plant.

Inasmuch as crown gall is analogous to animal cancer, as Smith (1911, 1912), Magnus (1918), Levine (1919, 1920), Levin and Levine (1920), and Jensen (1918) have pointed out, these results also have a bearing on the general question of feeding in cancer and a more specific relation to the question of the relation of general vigor and vitality to susceptibility.

The older literature concerning the crown gall of beets is too well known

<sup>1</sup> From the Department of Cancer Research of Montefiore Hospital, Dr. I. Levin, Chief

to need mention here. Only those papers that deal with the problem at hand are reviewed.

Tumor-like growths on the different varieties of beets have been recognized in America and Europe for a long time. These growths occur sporadically. Destructive epidemics are not known. Smith, Brown, and Townsend (1911) have shown that at least the gall formation known as crown gall<sup>2</sup> of the beet is produced by *Bacterium tumefaciens*. They were able to isolate the organism from the tumors on the beet and to infect beets, causing the formation of new crown galls.

Townsend (1915), studying the crown gall of the sugar beet which appears spontaneously in the field, concluded that the galls have no marked effect upon the size of the beet. The largest as well as the smallest beets may become seriously affected, and it is impossible to know whether roots would be large or small if they had been free from the infection. The galls begin to appear when the beets are one fourth to one half grown, that is, about midsummer; and from that time on they may appear at any time until harvest, so that crown galls of various sizes and ages may be found on the beets.

Jensen (1918) in his investigation of tumor-like growths in plants studied both spontaneous crown galls from the common races of beets and those that he produced experimentally by inoculation. He concludes that in the case of the mangel wurzel the crown gall has no detrimental effect upon the growth of the plant. In the garden beet, the tumor attains only slight size. In the sugar beet, on the other hand, Jensen finds the disease resulting in enormous tumor-like formations, irregular knotty structures which in section exhibit a very irregular arrangement of the vascular bundles differing markedly from that in the normal portion of the root. Jensen does not report on the relative sizes of the galls and roots in the sugar beet, nor does he discuss the structural characters of the normal roots of the various races for possible suggestions as to the cause of the differences in the size and structure of the galls.

#### MATERIALS AND METHODS

The cultivated garden varieties, Early Model, Egyptian Early, and Giant Mangel Wurzel of *Beta vulgaris* were studied in my experiments. A preliminary test of the effect of the soil on the size of the root and crown gall produced when the roots were inoculated with *Bacterium tumefaciens* was carried out in six-inch pots in which a mixture of Early Model and Egyptian Early seeds was planted. Four kinds of soil were used. Each kind was placed in 12 pots. The first group was filled with garden soil mixed with an abundance of manure that had been previously used for mushroom culture. The second contained a brown loam that was obtained

<sup>2</sup> "Tuberculosis" of beets is a tumor-like growth on beets produced by *Bacterium beticola* (Smith, Brown, and Townsend, 1911).

from a neighboring lot, and the third, a combination of equal parts of garden soil and manure and of the loam used in the second. The fourth group was filled with a medium sand used for building purposes. Three seedlings were planted in each pot. The pots were placed in boxes, and the spaces between the pots were filled with hay. The boxes were then placed in the open where they were exposed to the light all day. When the tap roots began to appear, the soil was gently removed from one side of each root, and, with a needle dipped in a culture of *Bacterium tumefaciens*, the root was pricked five to fifteen times. The soil was then returned and the plants were not disturbed again until the middle of October. Then they were carefully removed from the soil and studied. In each group of pots, some plants were left uninoculated to serve as controls.

Field studies were made in three plots 12 x 25 feet each. The first two, "E" and "W," consisted of soil well worked and thoroughly mixed with an abundance of manure. The third, "SW," consisted of a coarse sandy soil never used before and unfertilized. In early May, the plots "E" and "SW" were planted with a mixture of Early Model and Egyptian Early. The rows were thinned out in June, and in the latter part of July, when the tap roots began to appear, they were inoculated in the manner described above with young cultures of *Bacterium tumefaciens*. Each inoculated plant was labeled. An equally large number of uninoculated plants were left growing among the inoculated ones to serve as controls. The plots were equally well exposed to sunlight for the greater part of the day. They were similarly worked and watered. A considerable number of inoculated plants were gathered from time to time and fixed for a cytological study to be reported on at a later time.

Plot "W" was sown with the Giant Mangel Wurzel seeds and treated as the plots "E" and "SW" were.

#### RELATION OF THE SOIL QUALITY TO THE SIZE AND WEIGHT OF THE ROOT AND OF THE CROWN GALL

We may consider first the experiments in which the beets were grown in pots as described above. The effect of the crown gall on the total beet crop grown under these conditions is only suggestive since the number of our experiments was relatively small. The relation of the size and weight of the root to the size and weight of the crown gall is the point with which we are specially concerned.

In this series of experiments, as noted, a mixture of seeds of the garden beet varieties, Early Model and Egyptian Early, were grown in 48 six-inch pots in four different kinds of soil. In the first group, made up of 12 pots, the soil consisted of a mixture of manure that had previously been used for mushroom culture and an equal quantity of garden soil. The second group of pots were filled with a brown silt loam, the third group contained equal parts of manure and brown silt loam, and the fourth contained a medium sand.

TABLE 1. Effect of the soil on the weights<sup>3</sup> of the garden beet, *Beta vulgaris*, vars. *Early Model* and *Egyptian Early*, the roots of which were inoculated with *Bacterium tumefaciens*. Growing in pots containing "A" garden soil and manure, "B" brown silt loam, "C" manure and brown silt loam, "D" medium sand

No.	Pot A		Pot B		Pot C		Pot D	
	Fresh	Dry	Fresh	Dry	Fresh	Dry	Fresh	Dry
1.....	31.75	3.30	81.40	5.40	38.30	3.00	36.80	3.60
2.....	60.00	5.60	46.00	4.50	2.10	1.50	30.00	3.80
3.....	113.60	11.80	37.10	3.00	46.10	4.70	38.60	3.60
4.....	65.40	5.50	24.60	1.80	32.10	3.30	33.50	4.50
5.....	38.60	4.60	51.00	4.10	10.00	1.20	23.70	2.70
6.....	45.50	4.80	24.10	2.30	22.30	2.10	36.00	4.20
7.....	45.00	5.30	26.00	2.70	36.50	4.40	37.70	4.30
8.....	42.50	4.60	33.10	3.00	22.60	2.40	5.10	.90
9.....	67.50	5.30	19.10	1.40	5.70	1.20	8.70	.90
10.....	51.10	6.15	60.00	3.90	13.20	1.60	53.70	5.50
11.....	71.10	7.10	66.60	7.50	9.50	1.00	13.70	1.90
12.....	78.10	9.00	21.60	1.20	7.10	.80	9.00	2.10
13.....	49.60	4.50	17.00	1.50	32.50	2.80	14.90	2.30
14.....	25.50	2.20	9.50	1.60	51.00	5.00	24.00	2.10
15.....	13.20	1.80	34.00	3.50	74.00	8.40	20.00	2.60
16.....	33.90	3.10	19.00		66.70	7.80	33.00	corrections .80
17.....	36.30	3.60	22.50	1.70	22.50	2.20	24.10	5.50
18.....	22.40	2.50	27.50	2.60	55.80	4.40	3.70	3.60
19.....	13.80	1.30	10.30	corrections	12.40	1.80	6.00	
20.....					31.00	3.15		
21.....					27.80	2.90		
22.....				2.60	51.20	5.50		
23.....				8.60	16.00	1.80		
24.....				4.50	13.40	1.70		
25.....				2.70	10.00	1.00		
Totals...	904.85	92.05	630.40	63.00	728.70	75.65	452.20	53.50
Averages	46.57	4.73	33.17	3.316	29.14	3.02	23.80	2.81

The plants, three to four in each pot, were inoculated as described above with *Bacterium tumefaciens* on July 20, 1920. On October 9, 1920, the plants were removed from the soil, and the sizes and weights of the roots grown in the different soils were compared.

Figure 1 shows the general development of the plants as they appeared in the pots and represents two average pots from each group of twelve, of the varieties *Early Model* and *Egyptian Early*. "A" represents the plants grown in the garden soil with an abundance of manure, "B" the plants in the brown silt loam, "C" the plants in brown silt loam and manure, and "D" the plants grown in medium sand.

The plants grown in pot "A" (garden soil plus manure) are much larger than those in pots, "C" (brown silt loam and manure) and in "D" (sand), but the difference is not so marked between "A" (garden soil and manure) and "B" (brown silt loam). The leaves of the plants growing in pot "A" are somewhat larger and appear to be more numerous. While we

<sup>3</sup> Weights given in grams in all tables.



have no very reliable basis for measuring health or vitality quantitatively, it would be generally conceded that plants such as those represented in pot "A" are more vigorous and more healthy than those in pot "D."

On removing the plants from the soil, it was found that the size of the



FIG. 1, A, B, C, and D. Four pots filled with manure, brown silt loam, manure and brown silt loam, and sand, respectively.

leaves generally served as a good indication of the size of the roots. The roots whether inoculated or uninoculated were largest when grown in the soil and manure, smaller when grown in brown silt loam or in the combination of the loam and manure, and smallest when grown in sand.

The size and weight of the crown gall in each case was directly proportional to the size and weight of the root, as will be shown below. It is seen that the weight of the entire plant grown in the four different soils shows that those plants which were grown in soil rich in organic material were well nourished and attained the greatest weights while those grown in sand weighed less. Table 1 gives the fresh and dry weights of the entire plants grown in the four different soils with their roots inoculated with *Bacterium tumefaciens*. Representative plants with their infected roots from each group are shown in figure 2. Figure 2, "A" shows an infected root of a plant grown in garden soil mixed with an abundance of manure. "B" was grown in brown silt loam and manure. "C" was grown in brown silt loam, and "D" was grown in sand. As shown in table 1, the infected plants grown in pots containing garden soil and manure attained a fresh weight of 46.57 g. and a dry weight of 4.73 g., while plants grown in brown silt loam

were next highest with an average weight when fresh of 33.17 g. and a dry weight of 3.32 g., and the plants grown in a combination of loam and manure fell slightly short of the weights attained in the loam alone. The difference, however, is slight. A striking difference is seen in the proportionate size

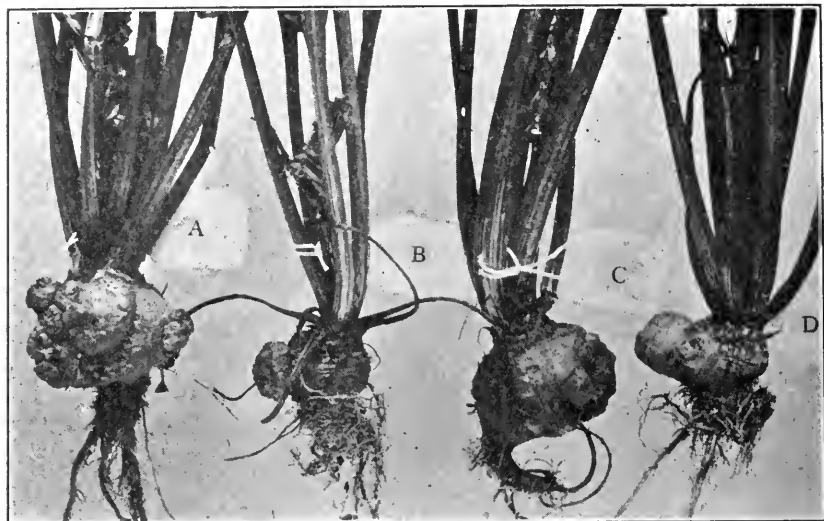


FIG. 2, A, B, C, and D. Roots of beets grown in pots filled with manure, manure and brown silt loam, brown silt loam, and sand respectively.

of the crown galls on the roots shown in figure 2, "A" and "D," and also in the average weights of the plants which are grown in the garden soil and sand respectively (see table 1). These results are quite striking and indicate rather clearly that the better nourished host responds to the parasitic infection more actively than the poorly nourished one, a fact which is generally recognized in animal pathology.

Better nutrition of the host does not tend to increased resistance to the growth of an inoculum of an animal tumor, but appears rather to have the contrary effect as shown by Ewing. It appears from these experiments that when the host is well fed the parasite is also well fed, it reproduces more actively, and produces a greater quantity of toxin which apparently calls forth relatively a greater hyperplasia of the host. The case is very clear here that normal development of the host rather favors the development of the crown gall. There is no evidence of increased resistance to the parasite in well grown as compared with poorly grown plants.

#### RESULTS OF THE FIELD EXPERIMENT

As mentioned above, similar seeds of *Beta vulgaris*, varieties Early Model and Egyptian Early, were planted in two plots, "E" and "SW," with an

area of 300 sq. ft. each. The first, "E," had been used during three previous seasons for root crops. The soil was well worked and abundantly treated with thoroughly rotted manure. The plot "SW" had never been used for a crop. It consisted of filled-in land. The soil was coarse and made up chiefly of coarse sand. No fertilizer was used on this plot. Beginning August 4 to 15, 1920, three hundred roots in each plot were inoculated with young cultures of *Bacterium tumefaciens* and labeled. A large number of beet roots growing among the inoculated plants were left undisturbed to serve as controls.



FIG. 3. A portion of plot "E" with the garden beet, one month after inoculating the root with *Bacterium tumefaciens*. The soil was well fertilized, and cultivated

A difference in the size of the plants in the plots "E" and "SW" appeared very early. Figure 3 shows a portion of plot "E." The leaves are not only larger but more numerous. The rows appear to be indistinct owing to the fact that the leaves cover the ground. The plants in the plot at the time this picture was made had been inoculated one month. The difference between plots "E" and "SW" was even more pronounced at the time the crop was harvested.

Figure 4 shows part of the plot "SW" with the poor soil. The plants

are relatively small and the leaves few. A considerable number of plants in this plot died. Here, also, the figure represents the condition of the plants in the plot one month after inoculation. An examination at this time of the roots of a few plants from plot "E," on good soil, showed that the inoculated plants had produced crown galls which were about the size of small hickory nuts, while those on the roots of the largest plants in poor



FIG. 4. A portion of plot "SW" with the garden beet, one month after inoculating the root with *Bacterium tumefaciens*; the soil was unfertilized and had never before been cultivated.

soil, plot "SW," were barely in evidence or at most had attained a size equal to that of a pea.

On examining the roots of the beets in October, when the entire group was harvested, the crown galls on the plants grown in the good soil, plot "E," were proportionately very large as compared to those on the roots of beets grown in plot "SW." Often the crown gall surrounded the entire upper portion of the root so that the normal contour of the root became indistinct. Figure 5 shows some typical roots with crown gall grown in good soil (plot "E").

The plants grown on poor soil (plot "SW") which were inoculated at about the same time as those growing in plot "E" were not only small,

but the crown galls were proportionately small as compared to the size of the root. Figure 7 represents a series of beet roots grown in plot "SW," photographed at maturity when the plants were harvested; in this series the smallest crown gall was smaller than a pea while the largest was about the size of a black walnut.

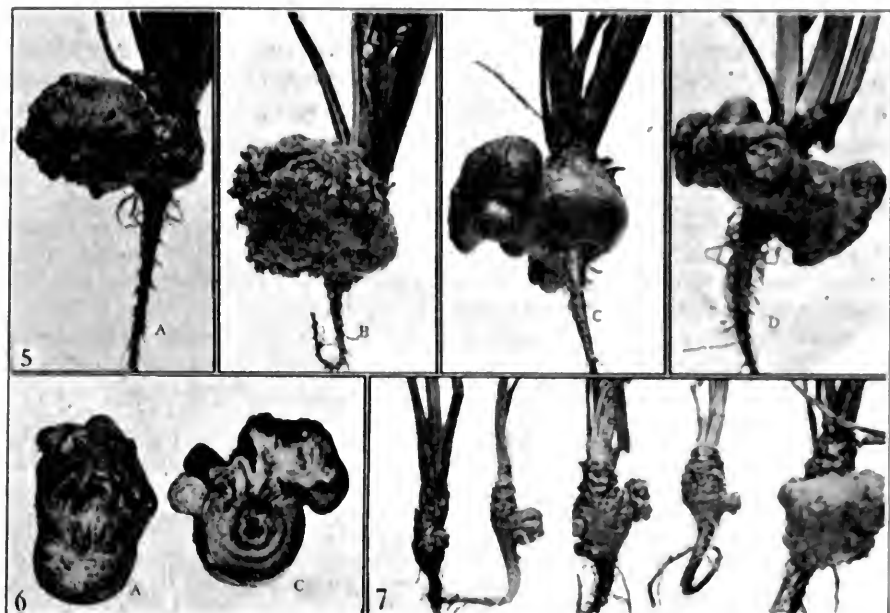


FIG. 5, A, B, C, D. A series of crown galls on the roots of the garden beet grown in fertilized soil; one month after inoculation. FIG. 6, A, C. Cross sections of the roots shown in figure 5, A and C. FIG. 7. A series of crown galls on garden beets grown in poor soil. Inoculation made August 11, 1920. Photographed October 16, 1920.

My observations on the appearance of the crown galls grown on these varieties of the garden beet are not in complete accord with those of Jensen, who claims that tumor-like growths on the different varieties of the garden beet differ from one another both in appearance and structure. In my cultures all the common types of crown gall appeared in each variety. Figure 5A represents the smooth type, 5B a warty gall, and 5C and 5D represent mixed types (smooth and warty), a form which Jensen does not recognize. In the mangel wurzel described below and shown in figure 9, we have similar types. The warty and the smooth types appear here as does the mixed type. It is of interest to note that crown galls of the smooth and warty types are also found in artificially produced crown galls on *Ficus elastica* (Levine, 1921.) The significance of these different types of crown gall is not yet perfectly understood.

In my observation of the galls on the Early Model and Egyptian Early

varieties, a number of smooth galls were found to be stemless as shown in figures 6A and 6C, which are cross sections of the beets shown in figures 5A and 5C respectively. The warty galls are as a rule stemless. The galls in the plants grown in plot "SW" were also of the three types, and the arrangement of the vascular bundles in the crown galls appears to depend upon the internal structure of the root before inoculation.

Shortly after the plants of the two plots "E" and "SW" were gathered they were carefully washed and weighed. They were loosely wrapped in separate pieces of paper and dried in a hot air oven at 100° C. for several days and then weighed again. The results are given in table 2. Columns 1 and 2 give the fresh and dry weights of the normal plants from plot "SW," that is, in the unfertilized soil.

TABLE 2. *Comparison of weights of Beta vulgaris, vars. Early Model and Egyptian Early, grown on plots "SW" and "E," the roots of which were inoculated with Bacterium tumefaciens; controls were growing among the inoculated plants. The inoculations were made August 4, 1920; the crop was harvested October 19, 1920*

Plants grown in Plot "SW" (unfertilized soil)					Plants grown in Plot "E" (fertilized soil)			
No.	Normal		Root Inoculated		Normal		Root Inoculated	
	Fresh	Dry	Fresh	Dry	Fresh	Dry	Fresh	Dry
1.....	5.90	.50	24.30	1.90	22.20	1.55	11.50	1.10
2.....	3.70	.45	17.50	1.50	27.60	2.15	33.10	3.90
3.....	5.30	.65	2.50	.20	18.80	1.20	38.40	3.10
4.....	5.50	.65	8.40	.70	47.2	3.70	21.10	2.05
5.....	9.50	1.45	19.40	1.50	24.30	2.10	29.30	25.05
6.....	7.60	.80	9.80	.70	17.20	1.70	61.60	5.30
7.....	9.00	1.00	8.50	.60	28.30	2.70	17.10	1.20
8.....	23.80	2.30	16.80	1.50	27.10	2.60	56.10	4.60
9.....	29.80	3.80	5.00	.60	28.80	7.70	38.10	3.90
10.....	9.00	1.30	8.10	.60	19.60	4.20	38.00	3.80
11.....	24.00	3.30	10.90	.90	54.50	3.00	26.00	2.70
12.....	14.00	1.40	5.00	.50	37.50	2.50	24.10	1.50
13.....	5.40	.90	4.30	.40	42.20	.90	44.00	2.70
14.....	4.50	.50	7.20	.80	9.10	2.25	96.10	6.50
15.....	2.40	.30	7.90	.70	23.40	1.55	20.10	1.40
16.....	6.00	.60	5.20	.50	21.70	2.80	42.10	3.25
17.....	11.20	1.30	6.80	.65	34.60	1.00	33.50	2.40
18.....	39.00	3.50			13.00	5.40	32.50	4.50
19.....	9.00	1.90			79.20	3.50	83.10	7.00
20.....	10.00	.90			46.80	3.40	25.70	2.70
21.....	8.00	1.70			20.60	1.10	18.10	1.50
22.....	12.90	1.90			18.00	2.90	37.60	2.90
23.....	20.00	.45			33.50	6.10	71.50	6.00
24.....	20.50				69.50	.70	21.80	1.70
25.....	4.60				9.70		18.50	1.65
26.....							72.10	6.50
27.....							28.50	2.45
28.....							36.10	2.60
29.....							16.00	1.10
Totals.....	301.50	31.55	167.60	14.25	774.40	66.10	1,091.60	115.05
Averages.....	12.06	1.26	9.85	.83	30.96	2.64	37.64	3.96

The average weight of the entire plants when fresh is 12.06 g. The average dry weight is 1.26 g. The uninoculated plants grown in plot "E," that is, in fertilized soil, attained an average weight of 30.96 g. with a dry weight of 2.64 g. (columns 5 and 6). The difference in the weights of the normal plants can be interpreted only as due to differences in the amounts of available food in the soil.

The uninoculated plants in both plots were, as noted, scattered among those that had been inoculated. The average weight of the inoculated plants grown in unfertilized soil (plot "SW") is less than that of the healthy plants (see table 2, columns 3 and 4). This difference in favor of the normal plant indicates that the presence of the parasite in these cases has lowered the total growth (tissue-producing capacity) of the plant.

A slight variation in the number and size of the leaves affects the total weights of the plants, yet the beet roots of the same variety bearing crown galls are always larger and weigh more than the normal roots grown under similar conditions. The marked difference in weight between the inoculated plants grown in plot "E" (fertilized soil, see table 2, columns 7 and 8) and the inoculated plants grown in plot "SW" is of considerable interest and not only indicates a difference in the nutritive conditions of the plants but confirms the data already obtained for these plants when grown in pots, and also supports the contention that the healthy plant responds to the influence of an invading organism more vigorously than does the poorly nourished or less robust plant.

These results further support the view maintained by many plant and animal pathologists that the response to an invading organism is greatest and that the parasite is most favored when the necessary metabolic processes of the host are satisfied.

#### THE WEIGHT OF THE CROWN GALL COMPARED WITH THE WEIGHT OF THE PLANT

I have further studied the weight of the crown-gall tumors from both the large and the small beets. The varieties used were Early Model, Egyptian Early, and Giant Mangel Wurzel. The plants in this experiment were grown under the most favorable conditions. When the tap roots had developed they were inoculated with *Bacterium tumefaciens* on August 4, 5, and 6, 1920, in the manner described above and were harvested October 15, 1920. An equally large number of plants among the inoculated ones were left to serve as controls. Figure 8 represents a portion of plot "W" in which the Giant Mangel Wurzel was growing.

For convenience, the crown gall was considered as that part of the root which could be separated from it by a stroke of the knife, continuous with the normal contour of the root. It is readily seen that this does not remove all the crown gall, for the neoplasia in the plant also invades the normal tissues, as Levin and Levine (1920) have shown for other plants, so that

the weights of the crown galls in tables 3 and 4 are somewhat below the actual weights; while the weights of the roots given in these tables are above the actual weights of the normal root tissue.

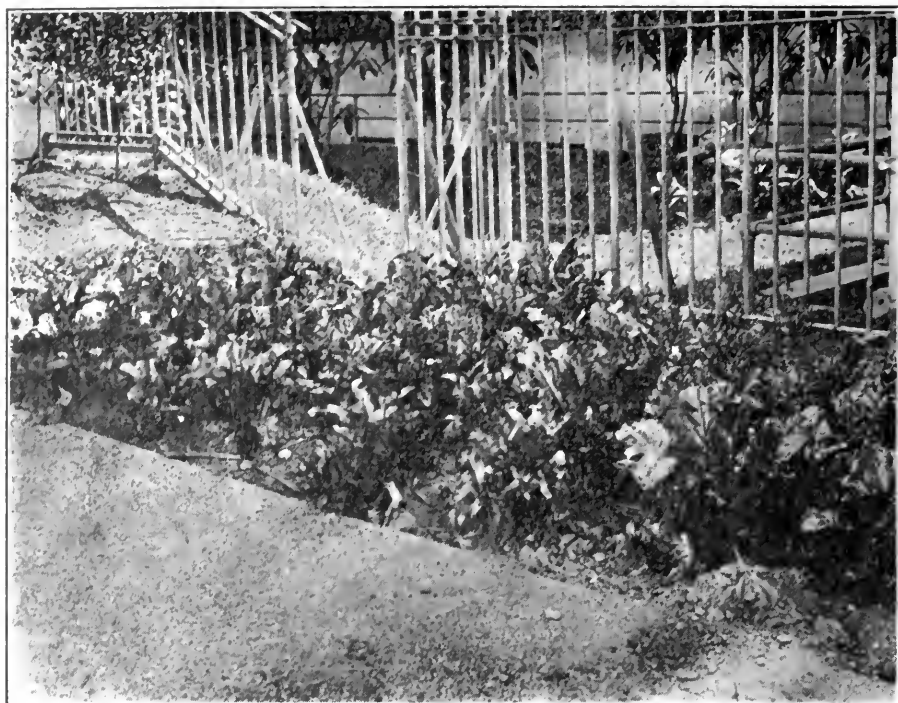


FIG. 8. A portion of plot "SW" showing the mangel wurzel, one month after the roots were inoculated with *Bacterium tumefaciens*.

The weight of the crown gall was determined by subtracting the weight of the plant, with the crown gall removed, from the weight of the entire plant. The weight of the leaves was determined by subtracting the weight of the root from that of the plant minus the crown gall.

The normal or uninoculated garden beet, varieties Early Model and Egyptian Early, showed an average weight of 39.49 g. (see table 3). The weight of the average normal root is 11.98 g., while that of the crown is 27.51 g. The entire weight of the average inoculated plant was 32.94 g., which is slightly below the normal weight. The average weight of these plants with the crown galls removed is 23.69 g., and the average weight of the crown galls is 9.25 g. The root without the crown gall averaged 8.61 g., the average weight of the crown gall and root is 17.86 g., which is above the average weight of the normal or uninoculated root. The decrease in size of the crown in the inoculated plants explains the difference in weight between the normal and the inoculated plants. I have not undertaken at



this time to explain the cause for the difference in these crowns. It may be suggested that possibly the disturbance of the vascular tissues of the root by the crown gall may be responsible for it, but no definite evidence is at hand.

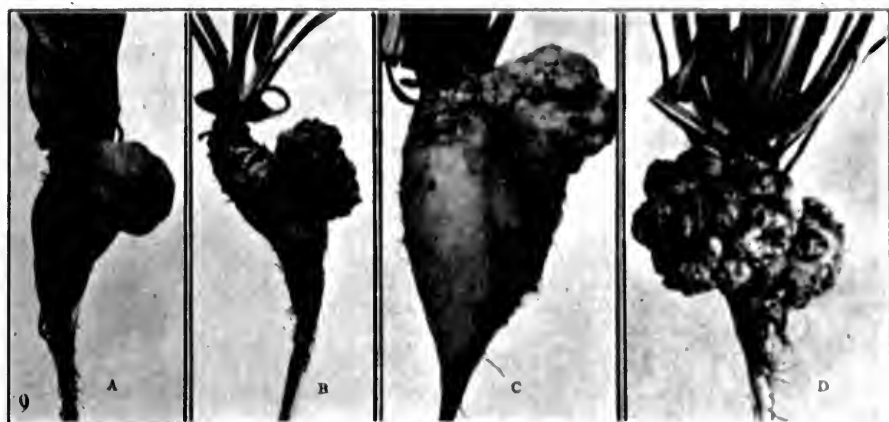


FIG. 9, A, B, C, D. Types of crown gall on the mangel wurzel: A, smooth; B, warty; C, smooth-warty condition combined; D, small smooth galls covered with clusters of warts

The weights of the inoculated and uninoculated mangel wurzel show similar conditions. The average weight of the uninoculated mangel wurzel grown in these cultures is 113.47 g. The weight of the root is 52.09 g., and the average weight of the crown is 61.38 g.

The average weight of the inoculated plants, samples of which are shown in figure 9 with the smooth, warty, and mixed galls, is 124.38 g. (see table 4), which is far above the average weight of the normal plant. The weight of the plant without the mass of the crown-gall tissue is 84.31 g., while that part of the crown gall that could be removed from the root averaged 39.91 g. The average weight of the root is 41.69 g. and of the crown 42.78 g. The average weight of the root and its crown gall is 81.6 g. Here again the crown gall increased the weight of the root as in the other cases mentioned above; while the weight of the leaves in the inoculated plants was considerably lower, the growth of the root overcame the difference so that the average weight of the entire inoculated plants was greater than that of the normal plants.

It may be of further interest to note that the crown galls in the mangel wurzel, harvested approximately two months after inoculation, weighed more than the remainder of the root. None of the crown gall tissue on the mangel wurzel had disintegrated at the time they were harvested, but on being brought into the laboratory and moistened, decay set in at once. The crown galls alone turned black, and within 48 hours they were disintegrating while the normal tissues of the root remained unchanged.

TABLE 3. *Weights of the leaf, root, and crown gall of Beta vulgaris, varieties Early Model and Egyptian Early, compared with the weight of the entire plant when grown under favorable conditions*

No.	Normal			Root Inoculated August 15, 1920		Harvested October 20, 1920		
	Total	Root	Leaf	Total	Without Gall	Gall	Root	Leaf
1.....	32.50	8.30		18.60	13.80		5.00	
2.....	137.70	33.80		52.50	30.60		6.80	
3.....	32.20	5.10		56.20	52.50		18.40	
4.....	10.00	3.00		19.00	11.70		5.60	
5.....	20.70	7.00		48.00	22.70		13.20	
6.....	19.10	2.50		108.80	100.90		18.00	
7.....	13.90	3.70		75.30	59.70		20.20	
8.....	22.20	2.20		57.40	47.80		23.40	
9.....	20.50	4.60		20.20	7.30		4.20	
10.....	16.70	3.00		13.90	13.00		2.10	
11.....	24.00	5.00		20.00	13.50		6.70	
12.....	13.50	4.20		30.00	19.50		6.00	
13.....	14.20	2.30		98.75	75.50		18.90	
14.....	160.00	29.70		27.50	15.30		6.10	
15.....	49.70	14.30		9.40	5.60		2.20	
16.....	71.70	13.90		23.60	15.60		5.10	
17.....	36.80	4.10		29.60	16.10		8.40	
18.....	15.90	2.90		93.00	64.30		35.50	
19.....	69.00	85.00		122.00	105.00		57.40	
20.....	9.50	5.00		72.20	54.20		17.85	
21.....				26.70	17.60		4.10	
22.....				17.80	9.00		2.90	
23.....				20.80	17.60		3.80	
24.....				37.10	30.70		6.90	
25.....				33.50	28.20		6.90	
26.....				18.40	11.80		14.40	
27.....				29.60	10.85		4.20	
28.....				17.60	9.60		6.50	
29.....				32.60	18.50		3.80	
30.....				42.70	37.30		5.70	
31.....				11.80	9.90		6.70	
32.....				23.00	20.30		2.90	
33.....				14.00	7.80		2.90	
34.....				19.30	15.90		1.60	
35.....				15.10	6.70		3.00	
36.....				59.00	47.60		3.70	
37.....				40.10	25.10		16.20	
38.....				38.40	16.30		18.00	
39.....				42.50	23.30		4.50	
40.....				31.30	22.50		6.70	
41.....				9.60	8.60		6.50	
42.....				11.70	11.00		4.70	
43.....				135.50	121.00		4.50	
44.....				20.90	18.20		19.90	
45.....				35.60	31.00		10.10	
46.....				38.00	29.00		16.00	
47.....				18.10	0.00		8.90	
48.....				45.60	24.30		3.50	
49.....				13.65	19.70		14.70	
50.....				46.60	34.10		15.40	
51.....				656.85	11.30		8.80	
52.....				21.50	24.90		5.95	
53.....				36.00	477.80		10.70	
54.....				13.70	9.60		175.05	

No.	Normal			Root Inoculated August 15, 1920		Harvested October 20, 1920		
	Total	Root	Leaf	Total	Without Gall	Gall	Root	Leaf
55.....				18.80	23.70		3.50	
56.....				23.50	8.00		5.80	
57.....				13.80	14.60		4.50	
58.....				12.80	12.00		7.80	
59.....				13.40	9.00		3.90	
60.....				22.05	8.90		4.00	
61.....				11.80	8.10		1.80	
62.....				37.50	17.35		3.30	
63.....				25.35	8.80		8.50	
64.....				12.90	27.40		3.40	
65.....				15.30	15.80		20.50	
66.....				15.30	9.50		2.70	
67.....				11.70	9.30		1.80	
68.....				17.70	11.10		3.40	
69.....				20.10	8.30		2.40	
70.....				15.50	9.50		4.00	
71.....				15.80	19.00		4.30	
72.....				18.00	8.60		4.20	
73.....				392.50	7.30		3.70	
74.....					9.70		1.45	
75.....					255.55		4.70	
76.....							99.65	
Total.....	789.80	239.60	550.20	2,405.30	1,729.70	675.60	628.65	1,101.05
Averages.....	39.49	11.98	27.51	32.94	23.69	9.25	8.61	15.08

## DISCUSSION OF RESULTS

The average weight of the root of the normal beet grown in fairly fertile soil is less than the average weight of the root of the same variety bearing a crown gall due to an artificial inoculation with *Bacterium tumefaciens* and grown under similar conditions. The average weight of the beets bearing crown galls and grown in pots filled with a garden soil and manure combination is greater than the average weight of the beets inoculated with *Bacterium tumefaciens* and grown in pots filled with sand. The average weight of the entire normal beet plants is greater or less than the average weight of the entire inoculated beet plant, depending upon the number of leaves on each. The leaves and crown of a normal beet plant weigh more than the leaves and crown of a plant of the same variety grown under similar conditions but whose root bears a crown gall. It is suggested that this difference in leaf development may be caused by interference with the distribution of food caused by the crown galls, although no direct evidence upon this question is available.

The evidence is clear that a well nourished, vigorously growing, and healthy host responds to the invasion of a parasite by a hypertrophy and a hyperplasia which are greater than result in the case of a poorly nourished or feebly growing host. These results are in agreement with the obser-

variations of other workers as to the relations of host and parasite in certain cases.

TABLE 4. *Relation of the weights of the leaf, root, and crown gall of the Giant Mangel Wurzel to the weight of the entire plant when grown under favorable conditions*

Normal				Roots Inoculated August 5, Harvested October 9, 1920				
No.	Total	Root	Leaf	Total	Without Gall	Gall	Root	Leaf
1	67.10	32.00	35.10	143.90	63.30		34.60	
2	123.40	68.10	55.30	50.30	33.70		28.70	
3	117.40	41.40	76.00	51.10	39.90		18.80	
4	102.80	37.40	65.40	45.70	21.30		14.20	
5	28.50	4.10	24.40	199.60	129.60		83.30	
6	76.60	14.30	62.30	250.80	170.30		80.20	
7	131.00	58.70	72.30	210.20	140.10		92.00	
8	81.05	55.60	25.45	135.90	96.80		42.90	
9	230.60	101.90	128.70	193.60	118.50		63.60	
10	114.40	38.50	75.90	51.10	36.40		21.10	
11	121.00	56.90	64.10	176.10	133.00		60.00	
12	226.30	144.50	81.80	163.70	76.60		37.80	
13	174.50	95.75	78.75	42.30	24.70		17.80	
14	75.00	35.50	39.50	111.80	60.80		22.20	
15	77.10	36.20	40.90	78.60	58.20		41.80	
16	82.40	32.30	50.10	85.60	61.05		39.10	
17	100.00	32.50	69.60	61.40	36.20		23.30	
18				58.90	40.80		26.00	
19				50.60	38.90		19.55	
20				86.40	38.70		22.70	
21				187.70	146.05		88.05	
22				86.70	78.40		32.70	
23				30.70	24.50		14.15	
24				38.20	37.70		16.10	
25				125.80	115.70		40.00	
26				190.00	116.35		73.55	
27				410.00	264.60		106.40	
28				31.05	25.80		15.20	
29				111.40	61.00		36.60	
30				152.90	109.00		43.50	
31				164.00	115.10		62.10	
32				121.30	89.20		51.00	
33				199.40	115.90		67.90	
34				83.35	57.10		28.00	
35				25.00	22.50		14.40	
36				110.60	73.00		44.30	
37				120.50	79.70		28.00	
38				32.40	24.00		13.00	
39				75.40	39.50		27.80	
40				209.40	142.30		47.00	
41				104.60	65.20		26.80	
42				57.40	34.70		27.00	
43				28.80	30.50		13.60	
44				178.00	84.00		65.50	
45				74.40	53.70		20.30	
46				25.60	13.20		2.80	
47				243.40	173.40		10.50	
48				211.50	186.00		122.00	
49				276.50	258.10		83.10	
50				154.50	135.30		43.85	
51				161.00	105.00		55.00	
52				200.90	137.70		97.05	

Normal				Roots Inoculated August 5, Harvested October 9, 1920				
No.	Total	Root	Leaf	Total	Without Gall	Gall	Root	Leaf
53.....				51.50	46.40		14.00	
54.....				118.40	64.20		38.70	
55.....				68.70	40.50		24.00	
56.....				137.60	103.10		42.10	
57.....				129.00	73.80		43.60	
58.....				198.60	123.40		62.90	
59.....				165.50	90.00		28.10	
Totals....	1,929.15	885.65	1,043.50	7,339.30	4,984.45	2,354.85	2,459.90	2,524.55
Averages ..	113.47	52.09	61.39	124.38	84.31	39.91	41.69	42.78

Spinks (1913) in his study of water and soil cultures of wheat and barley showed that these plants were more susceptible to *Puccinia glumarum* and *Erysiphe graminis* when the plants were provided with large amounts of available nitrogen. Plants which were semi-starved as regards nitrogen exhibited a considerable degree of so-called immunity. Peltier (1918) and Peltier and Frederick (1920) showed that in the case of citrus canker the hosts were more susceptible when placed in conditions that induced rapid and vigorous growth.

Fromme and Murray (1919), studying the angular leaf spot of tobacco, a bacterial disease, found that those factors which promote rapid and vigorous growth of the host favor the parasite, and again Thomas (1921), studying the relation of the health of the host *Apium graveolens* (celery) to infection with the fungus *Septoria apii*, observed that those conditions of temperature, feeding, etc., which favored the health of the host as evidenced by vigorous development also increased the number of infections on the leaves.

Crown gall is analogous to animal cancer, as maintained by Smith, Levin and Levine. In the case of animal cancer, Ewing holds that "good health appears to favor the growth of tumor grafts and poor conditions retard it," while Teague claims that he was able to transplant mammary carcinoma of dogs only in animals weakened with distemper. In this relation of host vigor to virulence of the disease, crown gall, potato wart, club root, and other plant diseases resulting in hypertrophy and hyperplasia which have not been studied from this point of view are analogous to animal cancer.

This does not argue for or against the parasitic origin of animal cancer, for while the end results in animal and plant cancers are analogous, the initial stimuli may be entirely different—parasitic, mechanical, or even chemical.

The correlative of this proposition is quite true also, for Miss Brown (1920) has showed that *Pestalozzia* sp. inoculated into *Sapodilla* may produce

a large swelling, apparently a crown gall, while in larch, hemlock, and blue spruce this organism produces blighting of the leaves and no galls.

Crown gall belongs in the great class of diseases involving hypertrophies and hyperplasias of the host tissue. The reaction of the host to the parasite in these cases is obvious and specific. In sharp contrast with these we have the great group of cases in which plants parasitized by fungous or bacterial parasites show susceptibility by lack of visible reaction. Their tissues become necrotic because of destruction by the invading parasite. Whether in the cases of crown gall, potato wart, club root, and many other diseases the reaction appearing in the form of neoplastic growths may be interpreted as actively protective, is a difficult question. The types of disease in the two cases are certainly sharply distinct in plants; the symptoms in the former indicating accelerated metabolic activity and growth, while in the second case we have necrosis such as the soft rots, dry rots, cankers, etc.

We need not accept the conception advanced by some plant pathologists that the better the health of the organism the greater the susceptibility to an invading parasite. Susceptibility implies a certain relative adaptation to serve as a substratum for the growth of the parasite. The data presented as to crown galls on beets do not bear on the question of susceptibility. Under the conditions described the beets all showed practically 100 percent susceptibility.\* It is, however, in my opinion clearly shown from the results described above that the invading parasite induces a visible reaction in direct proportion to the general health of the individual. The proliferation of cells in the region of the invasion depends upon the general vigor and capacity for growth of the host tissue. This is in marked contrast with those plant diseases in which disintegration of the tissues is the first obvious evidence of the presence of the parasitic germ.

#### SUMMARY

1. *Beta vulgaris*, varieties Early Model, Egyptian Early, and Giant Mangel Wurzel, were grown in different kinds of soil to test the effect of the soils on the growth, size, and weight of the root when artificially inoculated with *Bacterium tumefaciens*.

2. Of pot cultures with (1) garden soil with an abundance of manure, (2) brown silt loam and manure, (3) brown silt loam, and (4) medium sand, the largest average weight of plants was obtained in the garden soil. The crown galls were also the largest on these plants. The plants grown in sand weighed the least, were the smallest in size, and had the smallest crown galls.

3. Beets grown in open-air plots gave the same results. Those on the better soil were larger and heavier, and the crown galls on these roots were larger than those on beets grown in the poorer soil.

4. While the weight of the individual plants both inoculated and unin-

oculated varied widely, the average weight of the roots with crown gall was greater than the average weight of the normal or uninoculated roots in the same plot.

5. Three different types of crown gall were observed in *Beta vulgaris*, namely, the smooth type, the warty type, and a mixed type consisting of the warty and smooth types.

6. The reaction of the beet to crown gall depends upon the health of the beet; that is, with any given lot of seeds the extent of the reaction and the size of the crown gall depend ultimately upon the condition of the soil and upon other environmental factors.

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## MALIGNANCY OF THE CROWN-GALL AND ITS ANALOGY TO ANIMAL CANCER<sup>1</sup>

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### METHODS EMPLOYED IN THE INVESTIGATIONS

In 1907, Dr. E. F. Smith showed that the disease of plants called crown-gall—tumor-like in nature—could be reproduced artificially by an inoculation of a normal plant with a pure culture of a bacillus which he called *Bacterium tumefaciens*. Smith maintains that this or a similar disease can be produced only by this particular organism, that all other tumor-like formations observed in plants due to other parasites, like *Plasmodiophora brassicae*, are entirely different pathological entities, and that only crown-gall is a true plant tumor. In his estimation, this tumor is practically identical, biologically, with animal and human cancer. Since crown-gall is caused by the action of the bacterium described by him, he concludes in one of his recent articles that "to a biologist the conclusion is almost irresistible that human cancer must be due to a parasite and that one parasite may well be the cause of the most diverse forms, as we have seen to be the case in plants." This deduction is so sweeping in character, so far-reaching in its generalization, and the results of Dr. Smith's work have become so widely known and quoted by the medical profession that it has seemed to the writers to be desirable to renew his investigations, to analyze the material from the viewpoint of animal pathology, and to attempt to determine the true analogy between the crown-gall and animal cancer.

<sup>1</sup> Presented before the American Association for Cancer Research, June 14, 1919

The writers have inoculated with the pure culture of *Bacterium tumefaciens* the following plants: Growing tips, stems, petioles, and blades of *Rosa* (Rose), *Ricinus* (castor oil), *Pelargonium* (house geranium), *Lycopersicum* (tomato), *Nicotianum* (tobacco), *Helianthus* (sun-flower), *Bryophyllum calycinum* and *Ficus elastica* (India-rubber tree). Galls formed were fixed at various stages of development in Carnoy, Flemming strong,



FIG. 1. CROWN-GALL ON A STEM OF A RUBBER PLANT

Hermann, Merkle, and Bouin's solutions. The first fixation was found best suited for the more woody galls. After embedding in paraffin, the sections were cut from 5 to 30 micra in thickness, and were stained with Flemming's triple stain, methyl green counterstained with fuchsin, or Delafield's hematoxylin counterstained with eosin. The most satisfactory preparations were obtained by fixing with Carnoy solution and staining with gentian violet and safranin. In these preparations the cell walls stain a

beautiful deep violet, while the cytoplasm and chromatin material stain a much fainter purple. The nucleolus takes a bright ruby red color.



FIG. 2. *a*, CROWN-GALL ON A STEM OF A ROSE; WART-LIKE BENIGN GALL. *b*, LONGITUDINAL SECTION OF THE SAME STEM

The gross study of the material shows that in nearly every inoculated plant there developed a distinct crown-gall within one or two months after inoculation. Usually these galls grow slowly and are not very large in comparison with the size



FIG. 3. LONGITUDINAL SECTION OF A STEM OF RICINUS PLANT  
The gall is benign, the normal stem tissue is only displaced

of the plant itself. Figure 1 shows a gall which grew for over six months on a rubber plant; the plant itself is 6 feet high. Most frequently the gall grows out of the surface of the stem and does



FIG. 4. *a*, RICINUS PLANT INOCULATED AT THE APICAL PORTION OF THE STEM; SHOWS DWARFING OF THE PLANT. *b*, CONTROL PLANT

not seem to affect the rest of the plant (fig. 2). In other instances the growth displaces and distorts a part of the cortical area of the stem (fig. 3). Only in a small percentage of the inoculated

plants does the crown-gall affect the tissues of the plant more deeply. Figure 4 shows a photograph of the growing regions of two plants, one inoculated with the microorganism, and the other a normal control plant. While the latter grew up above the tip,



FIG. 5. PELARGONIUM

Shows necrosis of the inoculated part of the plant

the inoculated plant ceased to grow and became dwarfed, and the leaves drooped. At the same time, even in the inoculated plant, the lower part of the stem as well as the root apparently remained normal. Figure 5 presents an instance where the part of the plant above the point of inoculation, and even to a certain



degree below the point of inoculation, became necrotic. Cross (fig. 6) or longitudinal (fig. 7) sections of such plants show that these crown galls grow invasively, destroy and replace normal



FIG. 6. LONGITUDINAL SECTIONS OF TWO STEMS OF RICINUS PLANTS  
Show invasive growth of the gall and destruction of the normal stem tissue

plant tissue, and occasionally develop further along the length of the stem in a manner which produces the appearance of a secondary metastatic tumor above or below the primary growth (fig. 8).

In accordance with the findings of Smith, the writers have also observed in many instances the formation of small leafy shoots at the periphery of a crown-gall (figs. 9 and 10).

The microscopical analysis of the material shows that the crown-gall consists of a number of uniformly small, young, undifferentiated cells which contain a greater amount of cytoplasm

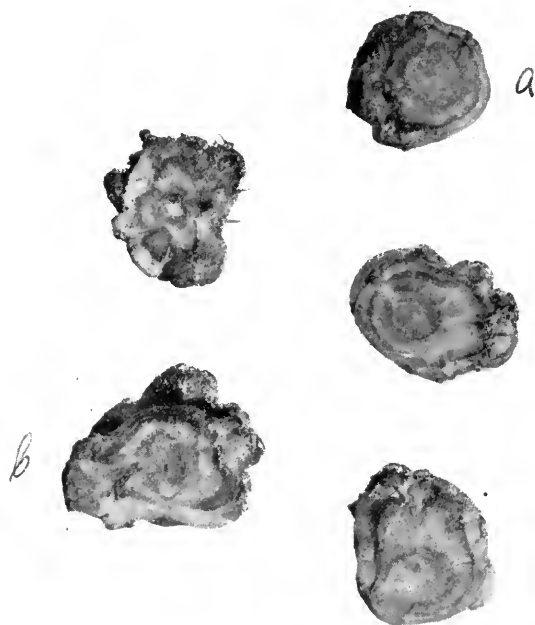


FIG. 7. CROSS SECTION SHOWING THE GRADUALLY INCREASING INVASION OF THE NORMAL STEM

The invasion is least at *a* and greatest at *b*

than the normal parenchyma cells within which they develop (fig. 11). The nuclei frequently show mitosis.

The small slowly growing crown-galls which frequently develop when the inoculation is done at the bases of leaves (fig. 12) present a very striking picture when examined microscopically. In the center of the growth there is an area of characteristic crown-gall cells, and surrounding this area the crown-gall cells appear

to be much larger in size and present all the characteristics of normal parenchyma cells (fig. 13). Apparently in these crown-galls the peripheral gall cells became differentiated into adult

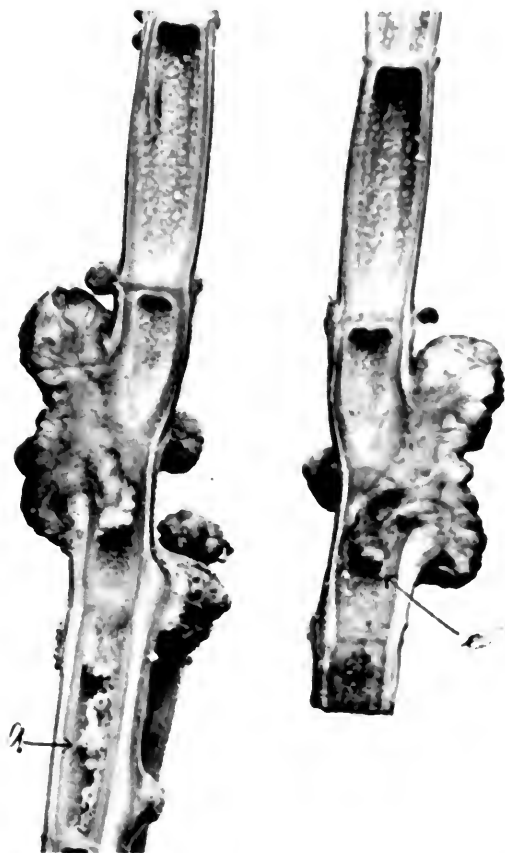


FIG. 8. LONGITUDINAL SECTIONS SHOWING AT *a* AND *b* CONDITIONS SOMEWHAT SIMILAR TO METASTASIS FORMATION

normal tissue cells. Frequently there were observed new irregular conducting systems formed within the crown-gall tissue (fig. 14), also apparently as a further differentiation of the crown-gall cells.

Microscopical study of a large number of the leafy sheets which developed at the periphery of a crown-gall showed that the starting point and the base of each leafy shoot is ordinary crown-gall



FIG. 9. LONGITUDINAL SECTION OF A STEM OF A TOBACCO PLANT

The apical portion of the stem was removed and the cut surface inoculated. The crown-gall shows the development of leafy shoots.

tissue with the identical gall cells (fig. 15), indicating that the crown-gall cells themselves gave rise to the formation of the leafy shoot.

## DISCUSSION

The analysis of the material shows that crown-gall is undoubtedly a *neoplastic disease* and that the pathogenesis of the condition consists in an abnormal proliferation of a group of cells.

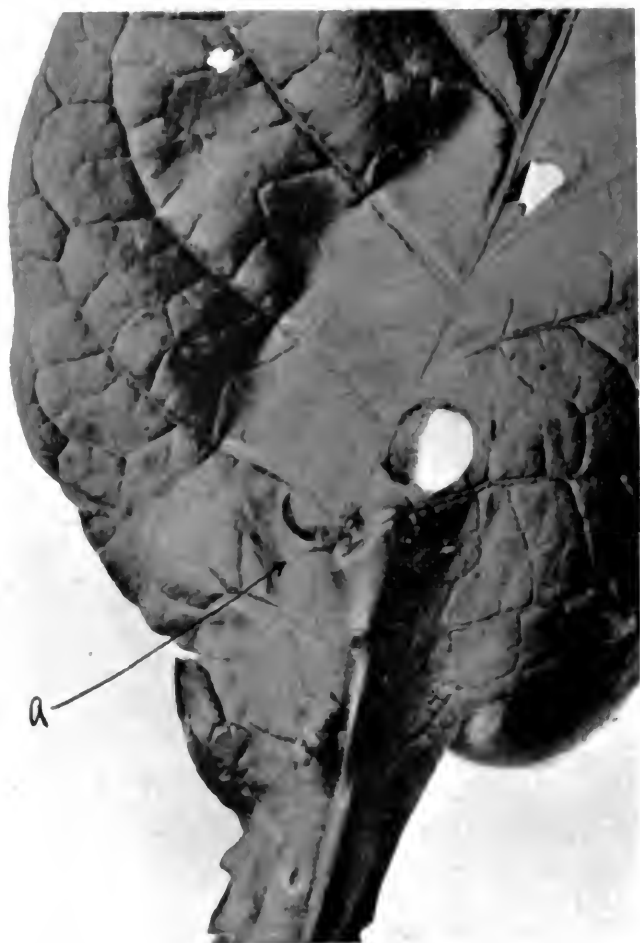


FIG. 10. TOBACCO LEAF INOCULATED AT THE MID RIB  
Shows at *a* a small gall with a leafy shoot

It is self-evident, therefore, that there must exist many points of analogy between the crown-gall and animal cancer. Since a

plant presents a much less complex organization than the animal, crown-gall tissue undoubtedly offers an ideal material for the study of the phenomena connected with cell proliferation. All this does not imply that crown-gall or any other neoplastic disease in animal or plant must of necessity be a tumor, even less so a malignant tumor—a cancer.

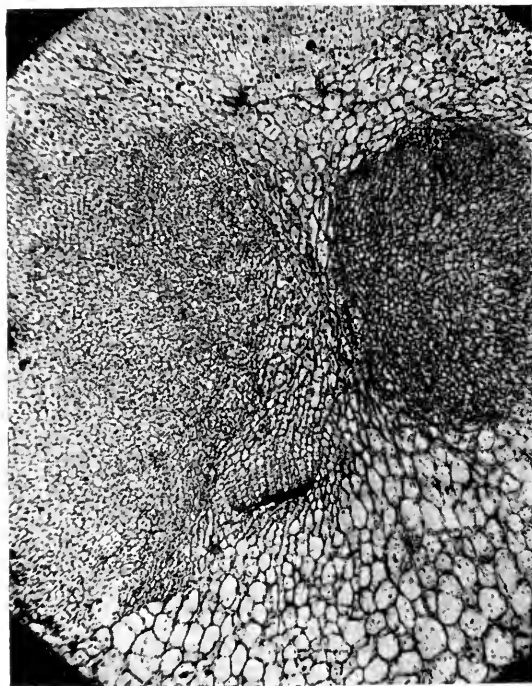


FIG. 11. MICROPHOTOGRAPH

Shows crown-gall tissue invading the normal stem tissue

In comparing new growth in animals and plants one must take into consideration the fact that an adult vertebrate is not capable of reproducing complete organs, while the highest plants may and do constantly reproduce with ease all their organs, leaves and branches as well as roots. Reproduction of parts of the organism, and consequently cell proliferation, is a function of an adult plant which may be induced with the greatest of ease.

It is self-evident that since an adult plant cell proliferates so as to reproduce an organ, a young crown-gall cell may do likewise. This characteristic of a normal plant cell explains the striking



FIG. 12. FOUR LEAVES OF RICINUS INOCULATED AT THE UPPER PORTION OF PETIOLES

Shows small wart-like galls

phenomenon, not encountered in any neoplastic disease in the animal, that a crown-gall may form within its own cells, or rather

as a transformation of its cells, not only adult differentiated tissues (parenchyma) but even rudimentary organs (conducting system) or a whole rudimentary organism (leafy shoot). All these various types of structures found in a crown-gall do not indicate, as appears to be the opinion of Smith, that the crown-gall is analogous to all the types of human cancer, but rather that it is different from any type of animal tumor.

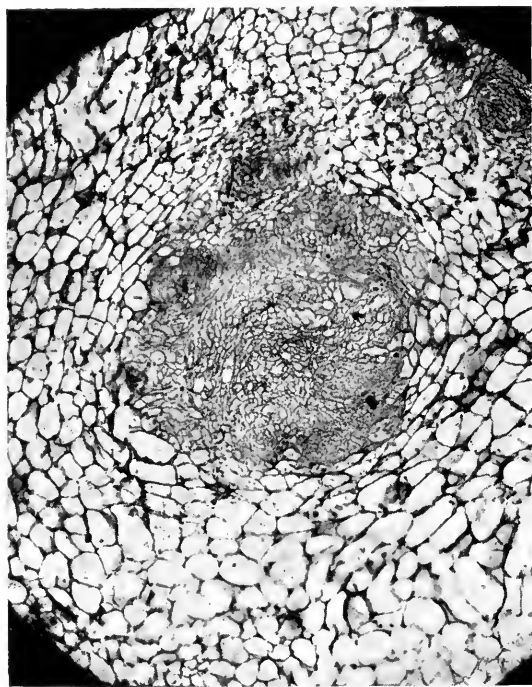


FIG. 13. MICROPHOTOGRAPH OF A GALL SHOWN IN FIGURE 12

The characteristic gall tissue is surrounded by newly formed parenchyma tissue.

In order to formulate clearly the position which the crown-gall occupies among the neoplastic diseases, one must take into consideration the fact that the crown-gall is usually a benign condition and only rarely does it act in a manner analogous to a malignant tumor in an animal.



The true mechanism of the formation of a benign crown-gall can be conceived only in the light of the difference in the structure of an animal and a plant organism. An animal organism reacts frequently to an attack of any injurious agent with the so-called inflammatory processes, which are accompanied by certain activities of the lymphoid tissues and proliferation and migrations of lymph cells. These cells, and not the special tissues of the injured region, offer protection, envelop and destroy the injurious



FIG. 14. MICROPHOTOGRAPH

Crown-gall showing newly formed irregular conducting system

agent, or neutralize it. When the latter is destroyed, the inflammatory process ceases and functions of repair or replacement of the injured tissue take place. This repair, which ends in the formation of a scar, is a type of neoplasia which differs radically from tumor formation. It continues just as long as is necessary to replace the lost tissue and then ceases; while tumor formation is a neoplasia which has no reason for its formation in the needs of the organism, and has no finality in its development.

The highest organized plants do not possess any specialized lymphoid tissue to take care of the functions of the protection of the organism against an injury or of the repair of the injured or lost tissue. One of the methods of protection of plants against injury consists in the presence of a cellulose wall. It seems plausible to suppose that as a matter of self-protection a plant may respond to an injury by a proliferation of the cells of the



FIG. 15. MICROPHOTOGRAPH

At *a* a crown-gall tissue, and at *b* the tissue of a leafy shoot

region which was subjected to the injury. The small wart-like galls, which grow very rapidly for a time and then remain stationary, as the writers have observed in a number of instances, are products of such functions of repair and protection and do not represent true tumors. That the *Bacterium tumefaciens* may be found even within the crown-gall cells or in the immediate neighborhood, still further emphasizes the truth of this conception.

Thus a small benign crown-gall is a condition analogous to granulation tissue and a scar in the animal organism. A crown-gall which grew to comparatively large size and still does not affect in any way the general welfare of the plant may be compared to a benign tumor in an animal, but is probably more nearly analogous to a large callus, which develops after a fracture of a long bone, or to a cheloid in the human.

Smith ascribes a great deal of importance to the phenomenon of development of leafy shoots in a certain number of crown-galls, and considers this type of gall to be identical with human embryoma. This finding he considers the main proof for his contention that all types of human cancer may be reproduced in plants by the aid of the *Bacterium tumefaciens*. In the opinion of the writers there is no analogy between a human embryoma and the crown-gall with a leafy shoot sprouting from it. An embryoma is a growth consisting of an irregular combination of various fetal tissues. It is more akin to a malformation than to a true tumor. A malignant tumor may develop subsequently within an embryoma in the same manner as it develops within normal tissue. The leafy shoot on the other hand appears on a fully developed crown-gall and is identical with a shoot which develops in a normal part of a plant. It simply indicates that crown-gall tissue as well as normal plant tissue may reproduce complete organs and thus still more widens the gap between the animal tumors and the crown-gall.

The malignant type of crown-gall is undoubtedly quite analogous to animal cancer. This condition occurs very rarely, as is seen from the results of the field studies on sugar beets of Townsend, who found that the destruction of the beets by the gall is not sufficient to influence the tonnage of the crop.

The most enthusiastic supporters of the parasitic theory of cancer admit that the formation of benign tumors cannot be due to a parasite. In other words, they admit that the mechanism of the formation of benign and malignant tumors must differ from each other. The same is undoubtedly true as regards the formation of the usual benign type of crown-gall and the by far less frequent condition when the gall dwarfs or destroys the plants

and thus acts as a malignant tumor. When two plants of the same size, the same age, growing in the same soil under identical conditions of heat, light, moisture and nutrition, are inoculated in the same regions with the same quantity of an identical culture of *Bacterium tumefaciens*, and there develops in one plant a small, benign, wart-like structure and in the other a large malignant tumor which may destroy the plant, it is difficult to conceive that the same microorganism, and only the microorganism, created the two conditions. The only possible explanation of the phenomenon lies in the fact that in the second plant, for some unknown reason, the cell proliferation which began only as a protection against the bacterial invasion and apparently ceased when the bacteria were rendered harmless, suddenly received an impetus for limitless proliferation. It seems then that the first impetus to the cell proliferation and formation of a benign crown-gall may be caused by the *Bacterium tumefaciens*. But the transformation of this protective or inflammatory benign cell proliferation into a malignant tumor is due, as in every type of animal and human cancer, to some mechanism within the organism of the host, independent of the microorganisms, the nature of which is unknown.

#### CONCLUSION

1. Crown-gall is a neoplastic disease, and offers an ideal material for the cytological study of cancer.
2. Crown-gall occurs both as a benign and a malignant condition.
3. The benign crown-gall is analogous to granuloma or cheloid in the human and is caused by *Bacterium tumefaciens*.
4. The malignant crown-gall is analogous to animal cancer, and *Bacterium tumefaciens* is not the direct cause of the malignant transformation.

152 (1734)

**Influence of radium and x-rays on the frog's leucocytes.**

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New York.]*

The white blood corpuscles are the most sensitive cells to the action of radium and x-rays. The senior writer has indicated in his previous publications that this action differs specifically for the various types of the white blood cells. This "selective" biological action of the rays goes even beyond the apparent structural differences of the cells. The rays for instance destroy rapidly the lymphocytes of lymphatic leukemia, while they have a comparatively slight effect on the lymphocytes in conditions of inflammatory leucocytosis. As a general rule the result of the action of radium and x-rays on the normal blood consists in the diminution of the number of lymphocytes and a relative increase in the number of the polymorphonuclear leucocytes. The other types of leucocytes usually remain unaffected.

The real significance of this phenomenon will remain obscured until a clearer insight is gained into the derivation and the comparative functional significance of the two types of white blood cells.

The numerical proportion of the lymphocytes and the polymorphonuclear leucocytes differs in the various animal species and it is therefore of great importance for the ultimate elucidation of the whole problem to test the action of the rays on different species of animals.

The present investigation consisted in subjecting to the action of radium and x-rays normal frogs and also frogs in whom a change in the white blood cells was induced by a preliminary injection of yeast.

*X-raying of Normal Frogs.*—The method consisted in taking a total and differential blood count of the animal before the raying. The whole animal was then x-rayed (45 minutes, Coolidge tube, 7 ma. 9-inch spark gap, 5-inch focal distance) and blood counts taken at various intervals for four days. The results obtained were as follows. The total leucocyte count showed practically no difference from the normal count before radiation, and the same holds true for the other series of experiments. The differential count showed a marked change in the numerical relationship between the polymorphonuclears and lymphocytes, while the number of the eosinophiles and transitionals remained practically stationary. To cite an instance,—2 eosin., 14 poly., 84 lympho. changed into 2 eosin., 70 poly., 28 lympho.

This change was most marked 24 hours after radiation, and the blood usually became normal after about four days.

*Radiumization of Normal Frogs.*—The method consisted in the introduction into dorsal lymph sac of a frog of a minute capillary glass tube about 4 mm. long containing from 1.0 to 0.6 millicuries of radium emanation. This method produces a slow and continuous action of the rays of radium on the organization of the animal. The results obtained on the blood were quite analogous to those produced by the x-rays. The important difference, however, consisted in the fact that the numerical difference between the lymphocytes was most pronounced only about three days after the insertion of the radium emanation capillary. For instance, the normal blood showed 1 eosin., 1 poly., 98 lympho.: 24 hours after radiumization, 2 eosin., 34 poly., 64 lympho., and 72 hours after radiumization 1 eosin., 85 poly., 13 lympho.

*Radiumization of Yeasted Frogs.*—The experiments consisted in the injection of an emulsion of yeast into a normal frog, and this was followed 24 hours later by x-raying the animal or an insertion of a radium emanation capillary. The injection of yeast is followed by a change in the blood of a frog similar to the one induced by the x-rays or radium, and the change is most marked 24 hours after the injection and continues for a few days. For instance, the normal blood showed 0 eosin., 18 poly., 82 lympho. 23 hours after yeasting, 1 eosin., 73 poly., 26 lympho. Now the

remarkable phenomenon observed in this series consisted in the fact that neither the x-rays nor the radium produced any further noticeable change in the numerical relationship between the lymphocytes and the polymorphonuclear leucocytes, or at the most a very slight additional decrease of lymphocytes. To cite an instance: the normal blood showed 2 eosin., 22 poly., 76 lympho.: 17 hours after yeasting, 0 eosin., 60 poly., 49 lympho. The animal was then x-rayed and immediately after showed 3 eosin., 68 poly., 29 lympho.: 24 hours later, 1 eosin., 80 poly., 19 lympho.

The analysis of the experiments shows that in the frog, as in the human, the action of the rays consists mainly in the diminution of the relative number of lymphocytes. However in the normal frog it does not seem to be accompanied by a noticeable change in the total blood count. The radiations seem to produce a different effect on lymphocytes of a normal frog from the one produced on the lymphocytes of a yeasted frog. This phenomenon is also analogous to effects which are related in the beginning of the paper as occurring in the human.





# PRACTICAL SUGGESTIONS ON REFRACTION.

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This paper details the method of taking the history and examining patients who come for relief from errors of refraction. It includes points to be particularly inquired into and methods of testing for the refractive error.

The work of the refractionist does not by any means consist of the mechanical examination of the eye with prescription of glasses. If properly done, it must take into consideration the numerous complexities which enter into the causation of ocular symptoms, whether local or general. All cases with ocular symptoms are not for the oculist; all ocular cases are not necessarily for prescription of glasses. Thus every case is a problem which must be solved, before any attempt to prescribe is made.

In taking the history, the following questions must be carefully gone into: Age, ocular symptoms, general health, amount of ocular work, conditions under which the work is done, the patient's habits, vision, condition of the ocular muscles (external and internal). A careful search for any pathologic changes should be made.

**AGE.** *Hypermetropia.* A healthy young individual may easily overcome a slight error without any eyestrain. Even a greater error may be overcome with or without symptoms. A very great error is generally accompanied only by poor vision (as no attempt constantly to correct is made). In the older patient, a slight or moderate error is corrected with symptoms of eyestrain. A greater error results only in poor vision, on account of the loss of power of accommodation. Presbyopes will get eyestrain, if they try to read without glasses, particularly in the early stage of their presbyopia, or when wearing too strong a correction.

*Myopia.* Myopes do not generally suffer from eyestrain, unless they have marked astigmatism, or when wearing an overcorrection. Myopia decreases with age. This is due to sclerosis, or flattening of the lens. High grade myopia may be progressive.

**OCULAR SYMPTOMS.** These consist of burning, itching, tearing, conjunctivitis, blepharitis, supraorbital pain, fronto-occipital pain, temporal head-

ache, rarely unilateral headache, gastric symptoms, vertigo, blurring of vision after prolonged reading, etc. Other causes for headache must be carefully considered. These may be: supraorbital neuralgia, sinusitis, gastrointestinal disturbance, anemia, cardiac disease, arteriosclerosis, uterine disease, alcohol, tobacco, bad atmospheric condition, etc. Headache caused by the eyes generally comes after use for near work, cinema, theater, shopping, etc. The headache is more frequent in the afternoon or evening. Rarely, the headache may not come till the next morning. Sometimes, in the presence of a marked error of refraction, the headache may be constant.

**GENERAL HEALTH** plays an important rôle in refractive errors. A patient may never feel any eyestrain until his general condition is below par. Glasses will relieve his eyestrain, but are frequently discarded when his health improves. Hypermetropes in good health require less correction than those in poor health.

**AMOUNT OF OCULAR WORK.** A good deal of near work, such as reading, writing, sewing, embroidering, will cause eyestrain even in the presence of a small hypermetropic error. In distant vision, driving an automobile, watching motion pictures, etc., will often be followed by eyestrain.

**CONDITIONS UNDER WHICH THE EYES ARE USED** will contribute toward the etiology of eyestrain. Thus poor light, artificial light, light coming from the wrong direction, glaring light, habit of holding the work too close to the eyes, reading of very small print.

**VISION.** Good vision means emmetropia, hypermetropia of slight or moderate degree, slight myopia, or moderate astigmatism. Poor vision means myopia, marked hypermetropia, or marked astigmatism. In older patients even a moderate hypermetropia may cause poor vision.

**CONDITION OF OCULAR MUSCLES**

This takes in principally exophoria, insufficient power of convergence, insufficient power of accommodation (asthenopia). In myopia exophoria is practically always present, but in spite of that, there is good power of convergence. When exophoria is present in the hyperope, convergence is generally insufficient. Such a condition may cause eyestrain and headache, which glasses will not correct, unless the exophoria is corrected by prisms or preferably by convergence or prism exercises. Hyperphoria will often cause headache, in spite of proper correction, unless a prism is used.

**PATHOLOGIC CHANGES** may account for poor vision and should, therefore, be carefully searched for. The most important of these are: opacities of the cornea and Descemet's membrane, changes in pupillary reactions, presence in the pupillary area of exudate on the anterior capsule of the lens, lenticular cataract, opacities in the vitreous, diseases of the choroid and retina, particularly in the region of the macula, diseases of the optic nerve. In the absence of evident pathologic changes, we must not forget toxic amblyopia, incipient glaucoma, congenital amblyopia and amblyopia ex anopsia.

**MANIFEST REFRACTION.** Examination of this is generally satisfactory in patients 40 years of age, or over. In younger patients, if starting with poor vision, we are able to get perfect vision with correction, it may not be necessary to go any further, prescribing the result of our manifest examination.

In *myopia* prescribe the weakest sphere that will give 20/20 vision with both eyes. In the presence of slight symptoms of eyestrain, with good vision, an *astigmatism* correction, especially when against the rule, may prove satisfactory. When no astigmatism is present, only apparent *hypermetropia*, retinoscopy should be resorted to; as also in all cases with marked symptoms of eyestrain, and when the manifest examination fails to give a satisfactory result. Children with poor vision or ocular symptoms should be retinoscoped after atropin has been used for three days.

The ophthalmometer is a useful guide in cases of astigmatism. It will indicate with fair accuracy the axis of

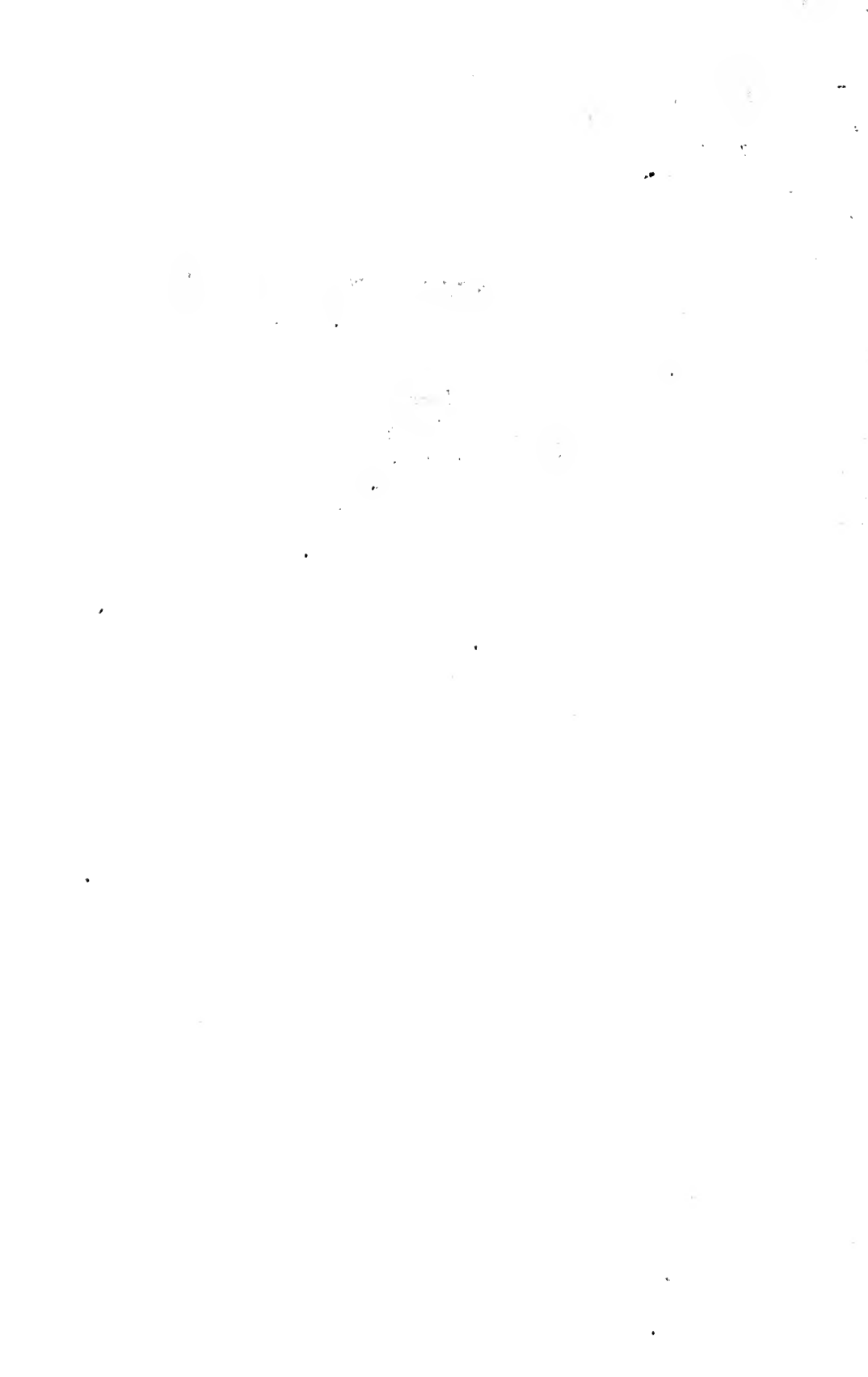
the cylinder. 0.75 seems to be the ophthalmometer finding for a normal cornea. 1.00 should indicate 0.25 with the rule; less than 0.75 would indicate astigmatism against the rule. It is a safe rule not to give a larger cylinder than the ophthalmometer indicates. Occasionally with a normal ophthalmometer reading (0.75) retinoscopy will show a slight lenticular astigmatism (0.25 to 0.50). Sometimes a high corneal astigmatism is counterbalanced by lenticular astigmatism and practically no astigmatism is indicated by the manifest examination or retinoscopy.

**RETINOSCOPY.** The degree of hypermetropic correction depends on the intensity of the symptoms and the age of the patient. The older patient requires more correction. The correction may vary from 0 to full correction. When in doubt make a postretinoscopic examination, particularly for near vision. Young hyperopes have strong power of accommodation, some of which they should be allowed to retain. The amount of correction should be in proportion to the degree of eyestrain and the amount of near work.

*Full correction* is given in the presence of convergent squint and when vision is poor owing to the loss of power of accommodation. The younger and healthier the patient, the less correction is required. Once a full correction is given, the patient becomes too dependent on his glasses. Patients with exophoria and weak convergence, if hypermetropic, should be given a weak correction until the exophoria is corrected by exercises, etc.

*Presbyopes* with exophoria should not be given a strong correction, and should be satisfied with a near point of 16 to 18 inches. Exophoria in presbyopes who have not used any glasses, or who have worn very weak correction, results from nonuse of convergence. Too much correction in the beginning will cause distress. In mixed astigmatism, correct vision first with cylinder; then, if a minus cylinder was used, treat the case like a hypermetropia; if a plus cylinder was used treat the case like a myopia. We choose the cylinder which will leave the weakest sphere to be used. Sometimes the sphere may be dispensed with.





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